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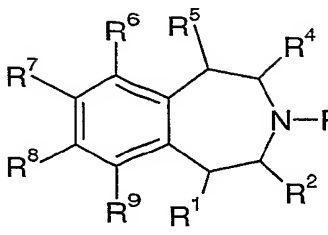
[Continued on next page]

(54) Title: 6-SUBSTITUTED 2,3,4,5-TETRAHYDRO-1H-BENZO[D]AZEPINES AS 5-HT2C RECEPTOR AGONISTS



(I)

(57) Abstract: The present invention provides 6-substituted 2,3,4,5-tetrahydro-1H-benzo[d]azepines of Formula I as selective 5-HT2C receptor agonists for the treatment of 5-HT2C associated disorders including obesity, obsessive/compulsive disorder, depression, and anxiety: I where: R6 is -C=C-R10, -O-R12, -S-R14, or -NR24R25; and other substituents are as defined in the specification.

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6-SUBSTITUTED 2,3,4,5-TETRAHYDRO-1H-BENZO[d]AZEPINES AS 5-HT_{2C} RECEPTOR AGONISTS

The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) has a rich pharmacology arising from a heterogeneous population of at least seven receptor classes. The serotonin 5-HT_2 class is further subdivided into at least three subtypes, designated 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}. The 5-HT_{2C} receptor has been isolated and characterized (Julius, *et al.*, U.S. Patent No. 4,985,352), and transgenic mice lacking the 5-HT_{2C} receptor have been reported to exhibit seizures and an eating disorder resulting in increased consumption of food (Julius *et al.*, U.S. Patent No. 5,698,766). The 5-HT_{2C} receptor has also been linked to various other neurological disorders including obesity (Vickers *et al.*, Psychopharmacology, 167: 274-280 (2003)), hyperphagia (Tecott *et al.*, Nature, 374: 542-546 (1995)), obsessive compulsive disorder (Martin *et al.*, Pharmacol. Biochem. Behav., 71: 615 (2002); Chou-Green *et al.*, Physiology & Behavior, 78: 641-649 (2003)), depression (Leysen, Kelder, Trends in Drug Research II, 29: 49-61 (1998)), anxiety (Curr. Opin. Invest. Drugs 2(4), p. 317 (1993)), substance abuse, sleep disorder (Frank *et al.*, Neuropsychopharmacology 27: 869-873 (2002)), hot flashes (EP 1213017 A2), epilepsy (Upton *et al.*, Eur. J. Pharmacol., 359: 33 (1998); Fitzgerald, Ennis, Annual Reports in Medicinal Chemistry, 37: 21-30 (2002)), and hypogonadism (Curr. Opin. Invest. Drugs 2(4), p. 317 (1993)).

Certain substituted 2,3,4,5-tetrahydro-1H-benzo[d]azepine compounds have been disclosed as useful therapeutics as for example:

US 4,265,890 describes certain substituted 2,3,4,5-tetrahydro-1H-benzo[d]azepine compounds as dopaminergic receptor antagonists for use as antipsychotics and antiemetics, *inter alia*.

EP 0 285 287 describes certain substituted 2,3,4,5-tetrahydro-1H-benzo[d]azepine compounds for use as agents to treat gastrointestinal motility disorders, *inter alia*.

WO 93/03015 and WO 93/04686 describe certain substituted 2,3,4,5-tetrahydro-1H-benzo[d]azepine compounds as alpha-adrenergic receptor antagonists for use as agents to treat hypertension and cardiovascular diseases in which changes in vascular resistance are desirable, *inter alia*.

WO 02/074746 A1 describes certain substituted 2,3,4,5-tetrahydro-1H-benzo[d]azepine compounds as 5-HT_{2C} agonists for the treatment of hypogonadism, obesity, hyperphagia, anxiety, depression, sleep disorder, *inter alia*.

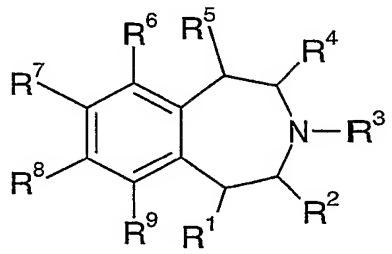
WO 03/006466 A1 describes certain substituted tricyclic hexahydroazepinoindole and indoline compounds as 5-HT ligands and consequently their usefulness for treating diseases wherein modulation of 5-HT activity is desired.

High affinity 5-HT_{2C} receptor agonists would provide useful therapeutics for the treatment of the above mentioned 5-HT_{2C} receptor-associated disorders including obesity, hyperphagia, obsessive/compulsive disorder, depression, anxiety, substance abuse, sleep disorder, hot flashes, and hypogonadism. High affinity 5-HT_{2C} receptor agonists that are also selective for the 5-HT_{2C} receptor, would provide such therapeutic benefit without the undesirable adverse events associated with current therapies. Achieving selectivity for the 5-HT_{2C} receptor, particularly as against the 5-HT_{2A} and 5-HT_{2B} receptors, has proven difficult in designing 5-HT_{2C} agonists. 5-HT_{2A} receptor agonists have been associated with problematic hallucinogenic adverse events. (Nelson *et al.*, Naunyn-Schmiedeberg's Arch. Pharm., 359: 1-6 (1999)). 5-HT_{2B} receptor agonists have been associated with cardiovascular related adverse events, such as valvulopathy. (V. Setola et al., Mol. Pharmacology, 63: 1223-1229 (2003), and ref. cited therein).

Previous references to substituted 2,3,4,5-tetrahydro-1H-benzo[d]azepine compounds as potential therapeutics have predominately recited their uses as alpha adrenergic and/or dopaminergic modulators. Adrenergic modulators are often associated with the treatment of cardiovascular diseases (Frishman, Kotob, Journal of Clinical Pharmacology, 39: 7-16 (1999)). Dopaminergic receptors are primary targets in the treatment of schizophrenia and Parkinson's disease (Seeman, Van Tol, Trends in

Pharmacological Sciences, 15: 264-270 (1994)). It will be appreciated by those skilled in the art that selectivity as against these and other physiologically important receptors will generally also be preferred characteristics for therapeutics for the specific treatment of 5-HT_{2C} associated disorders as described above.

The present invention provides selective 5-HT_{2C} agonist compounds of Formula I:



I

where:

R^1 is hydrogen, fluoro, or (C_1-C_3)alkyl;

R^2, R^3, and R^4 are each independently hydrogen, methyl, or ethyl;

R^5 is hydrogen, fluoro, methyl, or ethyl;

R^6 is -C≡C-R^{10}, -O-R^{12}, -S-R^{14}, or -$NR^{24}R^{25}$;

R^7 is hydrogen, halo, cyano, (C_1-C_6)alkyl optionally substituted with 1 to 6 fluoro substituents, (C_2-C_6)alkenyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl, (C_1-C_6)alkoxy optionally substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkylthio optionally substituted with 1 to 6 fluoro substituents, Ph^1-(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl-O-, or Ph^1-(C_0-C_3)alkyl-S-;

R^8 is hydrogen, halo, cyano, or –SCF_3;

R^9 is hydrogen, halo, cyano, -CF_3, –SCF_3, or (C_1-C_3)alkoxy optionally substituted with 1 to 6 fluoro substituents;

R^{10} is –CF_3, ethyl substituted with 1 to 5 fluoro substituents, (C_3-C_6) alkyl optionally substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ar^1-(C_0-C_3)alkyl, Ph^1-(C_0-C_3)alkyl, or 3-(C_1-C_4)alkyl-2-oxo-imidazolidin-1-yl-(C_1-C_3)alkyl;

R^{12} is Ph^2-$(C_1$-$C_3)$alkyl, Ar^2-$(C_1$-$C_3)$alkyl, $(C_1$-$C_6)$alkyl-S-$(C_2$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl-S-$(C_2$-$C_6)$alkyl, phenyl-S-$(C_2$-$C_6)$alkyl, Ph^2-S-$(C_2$-$C_6)$alkyl, phenylcarbonyl-$(C_1$-$C_3)$alkyl, Ph^2-C(O)-$(C_1$-$C_3)$alkyl, $(C_1$-$C_6)$alkoxycarbonyl$(C_3$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl-OC(O)-$(C_3$-$C_6)$alkyl, phenyloxycarbonyl-$(C_3$-$C_6)$alkyl, Ph^2-OC(O)-$(C_3$-$C_6)$alkyl, Ar^2-OC(O)-$(C_3$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl-NH-C(O)-$(C_2$-$C_4)$alkyl-, Ph^1-NH-C(O)-$(C_2$-$C_4)$alkyl-, Ar^2-NH-C(O)-$(C_2$-$C_4)$alkyl-, or R^{13}-C(O)NH-$(C_2$-$C_4)$alkyl;

R^{13} is $(C_3$-$C_7)$cycloalkyl$(C_0$-$C_3)$alkyl, Ph^1, Ar^2, or $(C_1$-$C_3)$alkoxy optionally substituted with 1 to 6 fluoro substituents, Ph^1-NH- or N-linked Het^1;

R^{14} is Ar^2 which is not N-linked to the sulfur atom, Ph^2, R^{15}–L-, tetrahydrofuranyl, tetrahydropyranyl, or phenyl-methyl substituted on the methyl moiety with a substituent selected from the group consisting of $(C_1$-$C_3)$-*n*-alkyl substituted with hydroxy, $(C_1$-$C_3)$alkyl-O-$(C_1$-$C_2)$-*n*-alkyl, $(C_1$-$C_3)$alkyl-C(O)-$(C_0$-$C_2)$-*n*-alkyl, and $(C_1$-$C_3)$alkyl-O-C(O)-$(C_0$-$C_2)$-*n*-alkyl,

wherein when R^{14} is Ph^2 or Ar^2, wherein Ar^2 is pyridyl, then R^{14} may also, optionally be substituted with phenyl-CH=CH- or phenyl-C≡C-,

said phenyl-CH=CH- or phenyl-C≡C- being optionally further substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, $(C_1$-$C_6)$alkyl optionally further substituted with 1 to 6 fluoro substituents, and $(C_1$-$C_6)$alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

wherein when Ar^2 is pyridyl, the pyridyl may alternatively, optionally be substituted with $R^{28}R^{29}$N-C(O)-, and optionally further substituted with one methyl, $-CF_3$, cyano, or $-SCF_3$ substituent, or with 1 to 2 halo substituents, and

wherein the tetrahydrofuranyl and tetrahydropyranyl may optionally be substituted with an oxo substituent, or with one or two groups independently selected from methyl and $–CF_3$;

R^{15} is $-OR^{16}$, cyano, $–SCF_3$, Ph^2, Ar^2, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, phthalimido, benzothiophenyl optionally substituted at the 2-position with phenyl or benzyl, benzothiazolyl optionally substituted at the 2-position with phenyl or benzyl,

benzothiadiazolyl optionally substituted with phenyl or benzyl, 2-oxo-dihydroindol-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-dihydroindol-5-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-imidazolidin-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-tetrahydropyrimidinyl optionally substituted at the 3 or 4 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-tetrahydroquinolin-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo- dihydrobenzimidazol-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, $-NR^{17}R^{18}$, $-C(O)R^{22}$, or a saturated heterocycle selected from the group consisting of pyrrolidinyl, piperidinyl, morpholinyl, and thiomorpholinyl, tetrahydrofuranyl, and tetrahydropyranyl,

wherein Ph^2 and Ar^2 when Ar^2 is pyridyl, may also optionally be substituted with phenyl-CH=CH- or phenyl-C≡C-,

said phenyl-CH=CH- and phenyl-C≡C- being optionally further substituted on the phenyl moiety with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

wherein Ar^2 may alternatively, optionally be substituted with a substituent selected from the group consisting of (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl, Het^1-(C_0-C_3)alkyl, pyridyl-(C_0-C_3)alkyl, and phenyl-(C_0-C_3)alkyl, and optionally further substituted with one methyl, $-CF_3$, cyano, or $-SCF_3$ substituent, or with 1 to 2 halo substituents,

said pyridyl-(C_0-C_3)alkyl and phenyl-(C_0-C_3)alkyl optionally being further substituted with 1-3 substituents independently selected from halo, $-CH_3$, $-OCH_3$, $-CF_3$, $-OCF_3$, -CN, and $-SCF_3$, and

wherein when Ar^2 is pyridyl, the pyridyl may alternatively, optionally be substituted with $R^{28}R^{29}N$-C(O)-, or (C_1-C_6)alkyl-C(O)- optionally substituted with 1 to 6 fluoro substituents, and may be optionally further substituted with one methyl, -CF_3, cyano, or -SCF_3 substituent, or with 1 to 2 halo substituents, and

wherein when Ar^2 is thiazolyl, the thiazolyl may alternatively, optionally be substituted with (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-NH-, and

wherein the pyrrolidinyl, piperidinyl, morpholinyl, and thiomorpholinyl is substituted with oxo- on a carbon atom adjacent to the ring nitrogen atom, or is N-substituted with a substituent selected from the group consisting of

(C_1-C_6)alkylcarbonyl, (C_1-C_6)alkylsulfonyl,
(C_3-C_7)cycloalkyl(C_0-C_3)alkyl-C(O)-,
(C_3-C_7)cycloalkyl(C_0-C_3)alkyl-$S(O)_2$-, Ph^1-(C_0-C_3)alkyl-C(O)-, and
Ph^1-(C_0-C_3)alkyl-$S(O)_2$-, and

may optionally be further substituted with 1 or 2 methyl or -CF_3 substituents, and when oxo-substituted, may optionally be further N-substituted with a substituent selected from the group consisting of (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, and Ph^1-(C_0-C_3)alkyl, and

wherein tetrahydrofuranyl and tetrahydropyranyl may optionally be substituted with an oxo substituent, and/or with one or two groups independently selected from methyl and –CF_3;

L is branched or unbranched (C_1-C_6)alkylene, except when R^{15} is -$NR^{17}R^{18}$ or Ar^2-N-linked to L, in which case L is branched or unbranched (C_2-C_6)alkylene, and when L is methylene or ethylene, L may optionally be substituted with gem-ethano or with 1 to 2 fluoro substituents, and when R^{15} is Ph^2, Ar^2, or a saturated heterocycle, L may alternatively, optionally be substituted with a substituent selected from the group consisting of hydroxy, cyano, -SCF_3, (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkoxycarbonyl optionally further substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkylcarbonyloxy optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-O-,

$(C_3$-$C_7)$cycloalkyl-$(C_0$-$C_3)$alkyl-O-C(O)-, and $(C_3$-$C_7)$cycloalkyl-$(C_0$-$C_3)$alkyl-C(O)-O-;

R^{16} is hydrogen, $(C_1$-$C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_1$-$C_6)$alkylcarbonyl, $(C_3$-$C_7)$cycloalkyl$(C_0$-$C_3)$alkyl, $(C_3$-$C_7)$cycloalkyl$(C_0$-$C_3)$alkyl-C(O)-, Ph^1-$(C_0$-$C_3)$alkyl, Ph^1-$(C_0$-$C_3)$alkyl-C(O)-, Ar^2-$(C_0$-$C_3)$alkyl, or Ar^2-$(C_0$-$C_3)$alkyl-C(O)-,

R^{17} is $(C_1$-$C_4)$alkyl optionally substituted with 1 to 6 fluoro substituents, *t*-butylsulfonyl, $(C_3$-$C_7)$cycloalkyl$(C_0$-$C_3)$alkyl-C(O)-, $(C_3$-$C_7)$cycloalkyl$(C_0$-$C_3)$alkyl-sulfonyl, Ph^1-$(C_0$-$C_3)$alkyl, Ph^1-$(C_0$-$C_3)$alkyl-C(O)-, Ph^1-$(C_0$-$C_3)$alkylsulfonyl, Ar^2-$(C_0$-$C_3)$alkyl, Ar^2-$(C_0$-$C_3)$alkyl-C(O)-, Ar^2-$(C_0$-$C_3)$alkylsulfonyl, $R^{19}OC(O)$-, or $R^{20}R^{21}NC(O)$-;

R^{18} is hydrogen or $(C_1$-$C_4)$alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{17} and R^{18}, taken together with the nitrogen atom to which they are attached form Het^1 where Het^1 is substituted with oxo- on a carbon atom adjacent to the ring nitrogen atom, or

R^{17} and R^{18}, taken together with the nitrogen atom to which they are attached, form an aromatic heterocycle selected from the group consisting of pyrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, and 1,2,4-triazolyl,

said aromatic heterocycle optionally being substituted with 1 to 2 halo substituents, or substituted with 1 to 2 $(C_1$-$C_4)$alkyl substituents optionally further substituted with 1 to 3 fluoro substituents, or mono-substituted with fluoro, nitro, cyano, $-SCF_3$, or $(C_1$-$C_4)$alkoxy optionally further substituted with 1 to 3 fluoro substituents, and optionally further substituted with a $(C_1$-$C_4)$alkyl substituent optionally further substituted with 1 to 3 fluoro substituents;

R^{19} is $(C_1$-$C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3$-$C_7)$cycloalkyl$(C_0$-$C_3)$alkyl, Ar^2-$(C_0$-$C_3)$alkyl, or Ph^1-$(C_0$-$C_3)$alkyl,

R^{20} is $(C_1$-$C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3$-$C_7)$cycloalkyl$(C_0$-$C_3)$alkyl, Ar^2-$(C_0$-$C_3)$alkyl, or Ph^1-$(C_0$-$C_3)$alkyl,

R^{21} is hydrogen or $(C_1$-$C_4)$alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{20} and R^{21}, taken together with the nitrogen atom to which they are attached, form Het^1;

R^{22} is $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl, R^{23}-O-, Ph^1-$(C_0\text{-}C_3)$alkyl, Ar^2-$(C_0\text{-}C_3)$alkyl, or $R^{32}R^{33}N$-;

R^{23} is $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl, Ph^1-$(C_0\text{-}C_3)$alkyl, or Ar^2-$(C_0\text{-}C_3)$alkyl;

R^{24} is $(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_5)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_1\text{-}C_6)$alkylthio$(C_2\text{-}C_5)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_1)$alkyl-O-$(C_1\text{-}C_5)$alkyl, $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_1)$alkyl-S-$(C_1\text{-}C_5)$alkyl, phenyl$(C_1\text{-}C_3)$ *n*-alkyl, Ph^2-$(C_1\text{-}C_3)$-*n*-alkyl, $Ar^2(C_0\text{-}C_3)$ *n*-alkyl, phenyl$(C_0\text{-}C_1)$alkyl-O-$(C_1\text{-}C_5)$alkyl, phenyl$(C_0\text{-}C_1)$alkyl-S-$(C_1\text{-}C_5)$alkyl, Ph^1-$(C_0\text{-}C_1)$alkyl-C(O)NH-$(C_2\text{-}C_4)$alkyl, Ph^1-$(C_0\text{-}C_1)$alkyl-NH-C(O)NH-$(C_2\text{-}C_4)$alkyl, pyridyl-$(C_0\text{-}C_1)$alkyl-C(O)NH-$(C_2\text{-}C_4)$alkyl, pyridyl-$(C_0\text{-}C_1)$alkyl-NH-C(O)NH-$(C_2\text{-}C_4)$alkyl, or $Ar^3(C_1\text{-}C_2)$alkyl,

where Ar^3 is a bi-cyclic moiety selected from a group consisting of indanyl, indolyl, dihydrobenzofuranyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzo[1,3]dioxolyl, naphthyl, dihydrobenzopyranyl, quinolinyl, isoquinolinyl, and benzo[1,2,3]thiadiazolyl,

said Ar^3 optionally being substituted with $(C_1\text{-}C_6)$alkyl optionally further substituted with 1 to 6 fluoro substituents, phenyl$(C_0\text{-}C_1)$alkyl optionally further substituted with 1 to 6 fluoro substituents, or substituted with $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl, or substituted with 1-3 substituents independently selected from the group consisting of halo, oxo, methyl, and $-CF_3$,

said phenyl$(C_1\text{-}C_3)$ *n*-alkyl, Ph^2-$(C_1\text{-}C_3)$ *n*-alkyl, or $Ar^2(C_0\text{-}C_3)$ *n*-alkyl optionally being substituted on the *n*-alkyl moiety when present with $(C_1\text{-}C_3)$alkyl, dimethyl, gem-ethano, 1 to 2 fluoro substituents, or $(C_1\text{-}C_6)$alkyl-C(O)-,

said $Ar^2(C_0\text{-}C_3)$ *n*-alkyl being alternatively optionally substituted with a substituent selected from the group consisting of $(C_3\text{-}C_7)$cycloalkyl-$(C_0\text{-}C_3)$alkyl, Het^1-$(C_0\text{-}C_3)$alkyl, pyridyl-$(C_0\text{-}C_3)$alkyl, phenyl-$(C_0\text{-}C_3)$alkyl, pyridyl-$(C_0\text{-}C_3)$alkyl-NH-, phenyl-$(C_0\text{-}C_3)$alkyl-NH-, $(C_1\text{-}C_6)$alkyl-S-, and

(C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-S-, and optionally further substituted with one methyl, -CF_3, cyano, or -SCF_3 substituent, or with 1 to 2 halo substituents,

said pyridyl-(C_0-C_3)alkyl and phenyl-(C_0-C_3)alkyl optionally being further substituted with 1-3 substituents independently selected from halo, -CH_3, -OCH_3, -CF_3, -OCF_3, -CN, and -SCF_3, and

said Ph^2-(C_1-C_3) *n*-alkyl and Ar^2(C_0-C_3) *n*-alkyl where Ar^2 is pyridyl, also optionally being substituted on the phenyl or Ar^2 moiety, respectively, with phenyl-CH=CH- or phenyl-C≡C-,

said phenyl-CH=CH- or phenyl-C≡C- being optionally further substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, -SCF_3, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

said Ar^2(C_0-C_3) *n*-alkyl where Ar^2 is pyridyl, alternatively, optionally being substituted with (C_1-C_6)alkyl-C(O)- or $R^{28}R^{29}$N-C(O)-, and optionally further substituted with one methyl, -CF_3, cyano, or -SCF_3 substituent, or with 1 to 2 halo substituents,

said phenyl(C_0-C_1)alkyl-O-(C_1-C_5)alkyl, or phenyl(C_0-C_1)alkyl-S-(C_1-C_5)alkyl optionally being substituted on the phenyl moiety with (C_1-C_2)-$S(O)_2$-, or with 1 to 5 independently selected halo substituents, or with 1 to 3 substituents independently selected from the group consisting of halo, cyano, –SCF_3, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

said pyridyl-(C_0-C_1)alkyl-C(O)NH-(C_2-C_4)alkyl and pyridyl-(C_0-C_1)alkyl-NH-C(O)NH-(C_2-C_4)alkyl optionally being substituted on the pyridyl moiety with methyl, -CF_3, or 1 to 3 halo substituents;

R^{25} is hydrogen, (C_1-C_3)alkyl optionally substituted with 1 to 6 fluoro substituents, or allyl;

R^{26} is hydrogen, $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl;

R^{27} is hydrogen or $(C_1\text{-}C_4)$alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{26} and R^{27}, taken together with the nitrogen atom to which they are attached, form Het^1;

R^{28} is $(C_1\text{-}C_8)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3\text{-}C_8)$cycloalkyl$(C_0\text{-}C_3)$alkyl, tetrahydropyran-3-yl$(C_0\text{-}C_3)$alkyl, tetrahydropyran-4-yl$(C_0\text{-}C_3)$alkyl, tetrahydrofuranyl$(C_0\text{-}C_3)$alkyl, Ph^1-$(C_0\text{-}C_2)$ *n*-alkyl, or Ar^2-$(C_0\text{-}C_2)$ *n*-alkyl,

said Ph^1-$(C_0\text{-}C_2)$ *n*-alkyl and Ar^2-$(C_0\text{-}C_2)$ *n*-alkyl optionally being substituted on the alkyl moiety when present with $(C_1\text{-}C_3)$alkyl, dimethyl, or gem-ethano;

R^{29} is hydrogen or $(C_1\text{-}C_3)$alkyl;

R^{30} is hydrogen, $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl, Ph^1-$(C_0\text{-}C_3)$alkyl, or $Ar^2(C_0\text{-}C_3)$alkyl,

R^{31} is hydrogen or $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{30} and R^{31}, taken together with the nitrogen atom to which they are attached, form Het^1,

said Het^1 also optionally being substituted with phenyl optionally further substituted with 1 to 3 halo substituents;

R^{32} and R^{33} are each independently hydrogen or $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{32} and R^{33}, taken together with the nitrogen atom to which they are attached, form Het^1, or R^{32} is $Ph^1(C_0\text{-}C_1)$alkyl provided that R^{33} is hydrogen;

Ar^1 is an aromatic heterocycle substituent selected from the group consisting of furanyl, thiophenyl, thiazolyl, oxazolyl, isoxazolyl, pyridyl, and pyridazinyl, any of which may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, $-CF_3$, $-O\text{-}CF_3$, nitro, cyano, and trifluoromethylthio;

Ar^2 is an aromatic heterocycle substituent selected from the group consisting of pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, furanyl, oxazolyl, isoxazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, thiophenyl, thiazolyl, isothiazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, pyridyl, pyridazinyl, and

benzimidazolyl, any of which may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and wherein pyridyl and pyridazinyl may also optionally be substituted with (C_1-C_6)alkylamino optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, or (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-amino;

Het^1 is a saturated, nitrogen-containing heterocycle substituent selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, morpholinyl, thiomorpholinyl, homomorpholinyl, and homothiomorpholinyl, any of which may optionally be substituted with (C_1-C_6)alkyl or with 2 methyl substituents;

Het^2 is a saturated, oxygen-containing heterocycle substituent selected from the group consisting of tetrahydrofuranyl and tetrahydropyranyl, any of which may optionally be substituted with (C_1-C_6)alkyl or with 2 methyl substituents;

Ph^1 is phenyl optionally substituted with 1 to 5 independently selected halo substituents, or with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents;

Ph^2 is phenyl substituted with:

a) 1 to 5 independently selected halo substituents; or

b) 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, nitro, hydroxy, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents; or

c) 0, 1, or 2 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, methyl, $-CF_3$, methoxy, $-OCF_3$, nitro, and hydroxy, together with one substituent selected from the group consisting of

i) (C_1-C_{10})alkyl optionally further substituted with 1 to 6 fluoro substituents or mono-substituted with hydroxy, (C_1-C_6)alkoxy, (C_3-C_7)cycloalkyl(C_0-C_3)alkyloxy, Het^2-(C_0-C_3)alkyloxy, Ph^1-(C_0-C_3)alkyloxy,

ii) $(C_1$-$C_{10})$alkoxy-$(C_0$-$C_3)$alkyl optionally further substituted with 1 to 6 fluoro substituents, and optionally further substituted with hydroxy,

iii) $(C_1$-$C_6)$alkyl-C(O)-$(C_0$-$C_5)$alkyl optionally further substituted with 1 to 6 fluoro substituents,

iv) carboxy,

v) $(C_1$-$C_6)$alkoxycarbonyl optionally further substituted with 1 to 6 fluoro substituents,

vi) $(C_1$-$C_6)$alkyl-C(O)-$(C_0$-$C_3)$-O- optionally further substituted with 1 to 6 fluoro substituents,

vii) $(C_1$-$C_6)$alkylthio-$(C_0$-$C_5)$alkyl optionally further substituted with 1 to 6 fluoro substituents,

viii) $(C_1$-$C_6)$alkylsulfinyl-$(C_0$-$C_5)$alkyl optionally further substituted with 1 to 6 fluoro substituents,

ix) $(C_1$-$C_6)$alkylsulfonyl-$(C_0$-$C_5)$alkyl optionally further substituted with 1 to 6 fluoro substituents,

x) $(C_1$-$C_6)$alkylsulfonyl-$(C_0$-$C_3)$alkyl-O- optionally further substituted with 1 to 6 fluoro substituents,

xi) $(C_3$-$C_7)$cycloalkyl$(C_0$-$C_3)$alkyl, optionally further substituted on the cycloalkyl with 1 to 4 substituents selected from methyl and fluoro,

xii) $(C_3$-$C_7)$cycloalkyl$(C_0$-$C_3)$alkyl-O-, optionally further substituted on the cycloalkyl with 1 to 4 substituents selected from methyl and fluoro,

xiii) $(C_3$-$C_7)$cycloalkyl$(C_0$-$C_3)$alkyl-C(O)-,

xiv) $(C_3$-$C_7)$cycloalkyl$(C_0$-$C_3)$alkyl-O-C(O)-,

xv) $(C_3$-$C_7)$cycloalkyl$(C_0$-$C_3)$alkyl-S-,

xvi) $(C_3$-$C_7)$cycloalkyl$(C_0$-$C_3)$alkyl-S(O)-,

xvii) $(C_3$-$C_7)$cycloalkyl$(C_0$-$C_3)$alkyl-$S(O)_2$-,

xviii) Ph^1-$(C_0$-$C_3)$alkyl, optionally substituted on the alkyl moiety with 1 to 2 fluoro substituents,

xix) Ph^1-$(C_0$-$C_3)$alkyl-O-, optionally substituted on the alkyl moiety with 1 to 2 fluoro substituents

xx) Ph^1-$(C_0$-$C_3)$alkyl-C(O)-,

xxi) Ph^1-(C_0-C_3)alkyl-O-C(O)-,

xxii) Ph^1-(C_0-C_3)alkyl-C(O)-(C_0-C_3)alkyl-O-,

xxiii) Ph^1-(C_0-C_3)alkylthio,

xxiv) Ph^1-(C_0-C_3)alkylsulfinyl,

xxv) Ph^1-(C_0-C_3)alkylsulfonyl,

xxvi) Ar^2(C_0-C_3)alkyl,

xxvii) Ar^2(C_0-C_3)alkyl-O-

xxviii) Ar^2-(C_0-C_3)alkyl-S-,

xxix) Ar^2(C_0-C_3)alkyl-C(O)-,

xxx) Ar^2(C_0-C_3)alkyl-C(S)-,

xxxi) Ar^2-(C_0-C_3)alkylsulfinyl,

xxxii) Ar^2-(C_0-C_3)alkylsulfonyl,

xxxiii) Het^1(C_0-C_3)alkyl-C(O)- optionally substituted on the Het^1 moiety with Ph^1,

xxxiv) Het^1(C_0-C_3)alkyl-C(S)- optionally substituted on the Het^1 moiety with Ph^1,

xxxv) N-linked Het^1-C(O)-(C_0-C_3)alkyl-O-,

xxxvi) Het^2-(C_0-C_3)alkyloxy,

xxxvii) $R^{26}R^{27}N$-,

xxxviii) $R^{28}R^{29}$-N-(C_1-C_3)alkoxy,

xxxix) $R^{28}R^{29}N$-C(O)-,

xl) $R^{28}R^{29}N$-C(O)-(C_1-C_3)alkyl-O-,

xli) $R^{28}R^{29}N$-C(S)-,

xlii) $R^{30}R^{31}N$-$S(O)_2$-,

xliii) HON=$C(CH_3)$-, and

xliv) HON=$C(Ph^1)$-,

or a pharmaceutically acceptable salt thereof, subject to the following provisos:

a) no more than two of R^1, R^2, R^3, R^4, and R^5 may be other than hydrogen;

b) when R^2 is methyl, then R^1, R^3, R^4, and R^5 are each hydrogen;

c) when R^3 is methyl, then R^2 and R^4 are each hydrogen;

d) when R^3 is methyl, R^7 and R^8 are each –OH, and R^1, R^2, R^4, R^5, and R^9 are each hydrogen, then R^6 is other than cyclohexylthio, furanylthio, or phenylthio; and

e) When R^{12} is Ar^2-(C_1-C_3)alkyl, then R^7 is other than hydrogen or R^9 is other than chloro.

This invention also provides pharmaceutical compositions which comprise a compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier, diluent, or excipient.

In another aspect of the present invention, there is provided a method for increasing activation of the 5-HT_{2C} receptor in mammals comprising administering to a mammal in need of such activation an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The present invention also provides a method for treating obesity in mammals comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The present invention also provides a method for treating obsessive/compulsive disorder in mammals comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

Furthermore, the present invention provides a method for treating depression in mammals comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

Furthermore, the present invention provides a method for treating anxiety in mammals comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

In preferred embodiments of the above methods of treatment utilizing a compound of Formula I, or a pharmaceutically acceptable salt thereof, the mammal is a human.

In another aspect of the present invention, there is provided a compound of Formula I for use in selectively increasing activation of the 5-HT_{2C} receptor and/or for use in treating a variety of disorders associated with decreased activation of 5-HT_{2C} receptors. Preferred embodiments of this aspect of the invention include a compound of Formula I for use in the treatment of obesity, hyperphagia, obsessive/compulsive disorder, depression, anxiety, substance abuse, sleep disorder, hot flashes, and/or hypogonadism. Particularly preferred embodiments of this aspect of the invention include the treatment of obesity, obsessive/compulsive disorder, depression, and/or anxiety.

In another aspect of the present invention, there is provided the use of one or more compounds of Formula I in the manufacture of a medicament for the activation of 5-HT_{2C} receptors in a mammal. In preferred embodiments of this aspect of the invention, there is provided the use of one or more compounds of Formula I in the manufacture of a medicament for the treatment of obesity, hyperphagia, obsessive/compulsive disorder, depression, anxiety, substance abuse, sleep disorder, hot flashes, and/or hypogonadism. Particularly preferred embodiments of this aspect of the invention include the use of one or more compounds of Formula I in the manufacture of medicaments for the treatment of obesity, obsessive/compulsive disorder, depression, and/or anxiety.

Additionally, the present invention provides a pharmaceutical formulation adapted for the treatment of obesity, or for the treatment of obsessive/compulsive disorder, or for the treatment of depression, or for the treatment of anxiety, each of which comprise a compound of Formula I in association with a pharmaceutically acceptable carrier, diluent or excipient.

In those instances where the disorders which can be treated by 5-HT_{2C} agonists are known by established and accepted classifications, their classifications can be found in various sources. For example, at present, the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV™) (1994, American Psychiatric

Association, Washington, D.C.), provides a diagnostic tool for identifying many of the disorders described herein. Also, the International Classification of Diseases, Tenth Revision (ICD-10), provides classifications for many of the disorders described herein. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for disorders described herein, including those as described in the DSM-IV and ICD-10, and that terminology and classification systems evolve with medical scientific progress.

The general chemical terms used throughout have their usual meanings. For example, the term "alkyl" refers to a branched or unbranched saturated hydrocarbon group. The term "*n*-alkyl" refers to an unbranched alkyl group. By way of illustration, but without limitation, the term "(C_1-C_2)alkyl" refers to methyl and ethyl. The term "(C_1-C_3) *n*-alkyl" refers to methyl, ethyl, and propyl. The term "(C_1-C_3)alkyl" refers to methyl, ethyl, propyl, and isopropyl. The term "(C_1-C_4) *n*-alkyl" refers to methyl, ethyl, *n*-propyl, and *n*-butyl. The term "(C_1-C_4)alkyl" refers to methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, *sec*-butyl, and *tert*-butyl. The term "(C_1-C_6)alkyl" refers to all branched and unbranched alkyl groups having from one to six carbon atoms. The term "(C_3-C_6)alkyl" refers to all branched and unbranched alkyl groups having from three to six carbon atoms. The term "(C_2-C_6)alkyl" refers to all branched and unbranched alkyl groups having from two to six carbon atoms.

(C_x-C_y)alkyl may also be used in conjunction with other substituents to indicate a branched or unbranched saturated hydrocarbon linker for the substituent, where x and y indicate the range of carbon atoms permitted in the linker moiety. By way of illustration, but without limitation, -(C_0-C_1)alkyl refers to a single bond or a methylene linker moiety; -(C_0-C_2)alkyl refers to a single bond, methylene, methyl-methylene, or ethylene linker moiety; -(C_0-C_3)alkyl further includes trimethylene, alpha- or beta-methyl ethylene, or ethyl methylene. -(C_1-C_2)alkyl, -(C_1-C_3)alkyl, -(C_1-C_4)alkyl, and -(C_1-C_6)alkyl refer to branched or unbranched alkylene linkers having from 1 to 2, 3, 4, or 6 carbons, respectively.

The term "alkenyl" refers to a branched or unbranched unsaturated hydrocarbon group. By way of illustration, but without limitation, the term "(C_2-C_6)alkenyl" refers to a branched or unbranched hydrocarbon group having from 2 to 6 carbon atoms and 1 or more carbon-carbon double bonds. Allyl means a propyl-2-en-1-yl moiety (CH_2=CH-CH_2-).

The term "(C_3-C_7)cycloalkyl" refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Cycloalkylalkyl refers to a cycloalkyl moiety linked through a branched or unbranched alkylene linker, as for example, but without limitation, -CH_2-, -CH_2CH_2-, -CH(CH_3)-, -$CH_2CH_2CH_2$-, -CH_2CH(CH_3)-, -CH(CH_3)CH_2-, -CH(CH_2CH_3)-, and the like. (C_3-C_7)cycloalkyl(C_0-$C_{1,\,2\ or\ 3}$)alkyl, refers to cycloalkyls linked through a single bond (i.e. C_0-alkyl) or an alkylene linker. Each alkyl, cycloalkyl, and cycloalkylalkyl group may be optionally substituted as provided for herein.

The terms "alkoxy", "phenyloxy", "sulfonyloxy", and "carbonyloxy" refer to an alkyl group, phenyl group, sulfonyl group, or carbonyl group, respectively, that is bonded through an oxygen atom.

The terms "alkylthio", "trifluoromethylthio", "cycloalkylthio" ("cyclohexylthio"), "phenylthio", and "furanylthio" refer to an alkyl group, trifluoromethyl group, cycloalkyl (cyclohexyl) group, phenyl group, or furanyl group, respectively, that is bonded through a sulfur atom.

The terms "alkylcarbonyl", "alkoxycarbonyl", "phenylcarbonyl", and "phenyloxycarbonyl", refer to an alkyl, alkoxy, phenyl, or phenyloxy group bonded through a carbonyl moiety.

The term "alkylcarbonyloxy" refers to an alkylcarbonyl group bonded through an oxygen atom.

The terms "(C_1-C_6)alkylsulfinyl", "Ph^1-(C_0-C_3)alkylsulfinyl", and "Ar^2-(C_0-C_3)alkylsulfinyl", refer to an alkyl, Ph^1-(C_0-C_3)alkyl, or Ar^2-(C_0-C_3)alkyl, respectively, group bonded through a sulfinyl moiety (-SO-).

The terms "alkylsulfonyl" (*t*-butylsulfonyl), "(C_3-C_7)cycloalkylsulfonyl", "phenylsulfonyl", "Ph^1-(C_0-C_3)alkylsulfonyl", and "Ar^2-(C_0-C_3)alkylsulfonyl", refer to an alkyl (*t*-butyl), (C_3-C_7)cycloalkyl, phenyl, Ph^1-(C_0-C_3)alkyl, or Ar^2-(C_0-C_3)alkyl group bonded through a sulfonyl moiety (-SO_2-).

The term "phenylamino" refers to a phenyl group bonded through a nitrogen atom.

The term "N-linked" means that the referenced moiety is linked through its nitrogen atom, by way of illustration, but without limitation, N-linked Het^1 means the Het^1 moiety is linked through a nitrogen atom in the ring of the Het^1 moiety, and N-linked Ar^2 means the Ar^2 moiety is linked through a nitrogen atom in the ring of the Ar^2 moiety.

The term "halo" refers to fluoro, chloro, bromo, or iodo. Preferred halo groups are fluoro, chloro, and bromo. More preferred halo groups are fluoro and chloro.

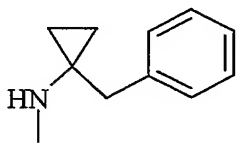
The term "heterocycle" is taken to mean a saturated or unsaturated 4 to 7 membered ring containing from 1 to 3 heteroatoms selected from nitrogen, oxygen and sulfur, said ring optionally being benzofused. Exemplary saturated heterocycles, for the purposes of the present invention, include azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, and the like. Exemplary unsaturated heterocycles include, but are not limited to, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, furanyl, oxazolyl, isoxazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, thiophenyl, thiazolyl, isothiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyridyl, pyridazinyl, and the like. Exemplary benzofused heterocyclic rings include, but are not limited to, indolyl, dihydroindolyl, indazolyl, benzisoxazolyl, benzimidazolyl, benzofuranyl, dihydrobenzofuranyl, benzoxazolyl, benzo[1,3]dioxolyl, benzothiophenyl, benzothiazolyl, quinolinyl, isoquinolinyl, benzopyranyl, dihydrobenzopyranyl, cinnolinyl, quinazolinyl

and the like, all of which may be optionally substituted as provided for herein, which also includes optionally substituted on the benzene ring when the heterocycle is benzofused.

In one embodiment, preferred heterocycles include pyrrolidinyl, piperidinyl, homopiperidinyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, isoxazolyl, 1,2,4-oxadiazolyl, thiophenyl, thiazolyl, 1,2,3-thiadiazolyl, pyridyl, pyridazinyl, indolyl, dihydroindolyl, benzimidazolyl, benzofuranyl, dihydrobenzofuranyl, benzoxazolyl, benzo[1,3]dioxolyl, benzothiophenyl, benzothiazolyl, quinolinyl, isoquinolinyl, and benzopyranyl, all of which may be optionally substituted as provided for herein.

In yet another embodiment, preferred heterocycles include pyridyl, pyridazinyl, and thiophenyl.

The terms "gem-", "geminal", or "geminate" refer to two identical substituents bonded to a common carbon atom, as for example, but without limitation, gem-methyl, meaning two methyl groups bound to a common carbon atom, as for instance in a 3,3-dimethyltetrahydrobenzofuranyl group. For the purposes of this application, gem-ethano means an ethylene substituent wherein both carbons are bound to the same carbon atom of the substituted group to form a cyclopropyl moiety, as for example, but without limitation, the ethano substituent on the 2-phenyl-(1,1-ethano)ethylamino group below:



It is to be understood that when a basic definition of a group lists optionally allowable substituents, and in another place that group is said to also optionally be substituted with other recited substituents, then those other recited substituents are intended to be added to the list of optionally allowable substituents listed in the basic definition of the group. Conversely, if in another place that group is said to be alternatively, optionally substituted with other recited substituents, then those other recited substituents are intended to replace the list of optionally allowable substituents

recited in the basic definition of the substituent. For example, but without limitation, Ar^2 has a basic definition that recites that any of the listed heteroaromatic groups may "optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and wherein pyridyl and pyridazinyl may also optionally be substituted with (C_1-C_6)alkylamino optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, or (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-amino." This is to be understood to mean that any of the listed heteroaromatic groups may optionally be substituted with [1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents], and that when Ar^2 is selected to be pyridyl or pyridazinyl, the list of substituents selectable for the 1 to 3 substituents is expanded to also include [(C_1-C_6)alkylamino optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, and (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-amino]. Likewise, in the definition of R^{14}, the terminology "wherein . . . Ar^2, wherein Ar^2 is pyridyl, then R^{14} may also, optionally be substituted with phenyl-CH=CH- or phenyl-C≡C- . . ." is understood to mean that the list of substituents selectable for the 1 to 3 substituents optionally allowed on Ar^2 = pyridyl is again expanded to also include [phenyl-CH=CH- or phenyl-C≡C- . . .]. Conversely, later in the definition of R^{14}, the terminology "wherein when Ar^2 is pyridyl, the pyridyl may alternatively, optionally be substituted with $R^{28}R^{29}N$-C(O)- and optionally further substituted with one methyl, $-CF_3$, cyano, or $-SCF_3$ substituent, or with 1 to 2 halo substituents", is understood to mean that when R^{14} is selected to be Ar^2 = pyridyl, then the list of 1 to 3 independently selected substituents optionally allowable in the basic definition of Ar^2 may be superceded by "$R^{28}R^{29}N$-C(O)- and optionally further substituted with one methyl, $-CF_3$, cyano, or $-SCF_3$ substituent, or with 1 to 2 halo substituents."

The term "amino protecting group" as used in this specification refers to a substituent commonly employed to block or protect the amino functionality while reacting other functional groups on the compound. Examples of such amino protecting groups

include the formyl group, the trityl group, the acetyl group, the trichloroacetyl group, the trifluoroacetyl group, the chloroacetyl, bromoacetyl, and iodoacetyl groups, carbamoyl-type blocking groups such as benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl ("FMOC"), *t*-butoxycarbonyl (*t*-BOC), and like amino protecting groups. The species of amino protecting group employed is not critical so long as the derivatized amino group is stable to the conditions of subsequent reactions on other positions of the molecule and can be removed at the appropriate point without disrupting the remainder of the molecule. The selection and use (addition and subsequent removal) of amino protecting groups is well known within the ordinary skill of the art. Further examples of groups referred to by the above terms are described by T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", 3rd edition, John Wiley and Sons, New York, NY, 1999, chapter 7, hereafter referred to as "*Greene*".

The term "pharmaceutical" or "pharmaceutically acceptable" when used herein as an adjective, means substantially non-toxic and substantially non-deleterious to the recipient.

By "pharmaceutical composition" it is further meant that the carrier, solvent, excipients and/or salt must be compatible with the active ingredient of the composition (e.g. a compound of Formula I). It is understood by those of ordinary skill in this art that the terms "pharmaceutical formulation" and "pharmaceutical composition" are generally interchangeable, and they are so used for the purposes of this application.

The term "effective amount" means an amount of a compound of Formula I which is capable of activating 5-HT_{2C} receptors and/or elicit a given pharmacological effect.

The term "suitable solvent" refers to any solvent, or mixture of solvents, inert to the ongoing reaction that sufficiently solubilizes the reactants to afford a medium within which to effect the desired reaction.

It is understood that compounds of the present invention may exist as stereoisomers. As such, all enantiomers, diastereomers, and mixtures thereof, are included within the scope of the present invention. Where specific stereochemistries are

identified in this application, the Cahn-Prelog-Ingold designations of (R)- and (S)- and the cis and trans designation of relative stereochemistry are used to refer to specific isomers and relative stereochemistry. Known optical rotations are designated by (+) and (-) for dextrorotatary and levorotatary, respectively. Where a chiral compound is resolved into its isomers, but absolute configurations or optical rotations are not determined, the isomers are arbitrarily designated as isomer 1, isomer 2, etc. While all enantiomers, diastereomers, and mixtures thereof, are contemplated within the present invention, preferred embodiments are single enantiomers and single diastereomers.

It is generally understood by those skilled in this art, that compounds intended for use in pharmaceutical compositions are routinely, though not necessarily, converted to a salt form in efforts to optimize such characteristics as the handling properties, stability, pharmacokinetic, and/or bioavailability, etc. Methods for converting a compound to a given salt form are well known in the art (see for example, Berge, S.M, Bighley, L.D., and Monkhouse, D.C., *J. Pharm. Sci.*, 66:1, (1977)). In that the compounds of the present invention are amines and therefore basic in nature, they readily react with a wide variety of pharmaceutically acceptable organic and inorganic acids to form pharmaceutically acceptable acid addition salts therewith. Such salts are also embodiments of this invention.

Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric, metaphosphoric, pyrophosphoric acid, and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanoic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include chloride, bromide, iodide, nitrate, acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, isobutyrate, phenylbutyrate, α-hydroxybutyrate, butyne-1,4-dicarboxylate, hexyne-1,4-dicarboxylate, caprate, caprylate, cinnamate, citrate, formate, fumarate, glycolate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, nicotinate, isonicotinate, oxalate, phthalate, terephthalate,

propiolate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, benzenesulfonate, p-bromobenzenesulfonate, chlorobenzenesulfonate, ethylsulfonate, 2-hydroxyethylsulfonate, methylsulfonate (mesylate), naphthalene-1-sulfonate, naphthalene-2-sulfonate, naphthalene-1,5-sulfonate, p-toluenesulfonate, xylenesulfonate, tartrate, and the like.

It is well known that such compounds can form salts in various molar ratios with the acid to provide, for example, the hemi-acid, mono-acid, di-acid salt, etc. Where in the salt formation procedure, the acid is added in a specific stoichiometric ratio, unless otherwise analyzed to confirm, the salt is presumed, but not known, to form in that molar ratio. Terms such as "$(acid)_x$" are understood to mean that the molar ratio of the salt formed is not known and can not be presumed, as for example, but without limitation, $(HCl)_x$ and $(methanesulfonic\ acid)_x$.

Abbreviations used herein are defined as follows:

"2B-3 ethanol" means ethanol denatured with toluene.

"AIBN" means 2,2'-azobisisobutyronitrile.

"Anal. Calc'd" or "Anal. Calcd" means calculated elemental analysis.

"APCI" means atmospheric pressure chemical ionization.

"bp" means boiling point.

"BINAP" means *rac*-2,2'-bis(diphenylphosphino)-1,1'binaphthyl.

"Boc" or "*t*-Boc" means *tert*-butoxycarbonyl.

"Brine" means a saturated aqueous sodium chloride solution.

"CV" means calorific value of oxygen.

"DBU" means 1,8-diazabicyclo[5.4.0]undec-7-ene.

"DCE" means 1,2-dichloroethane.

"DCM" means dichloromethane (i.e. methylene chloride, CH_2Cl_2).

"DIBAL-H" means diisobutylaluminum hydride.

"DIEA" means *N*,*N*-diisopropylethylamine.

"DMAP" means 4-(dimethylamino)pyridine.

"DME" means 1,2-dimethoxyethane.

"DMEA" means *N*,*N*-dimethylethylamine.

"DMF" means *N,N*-dimethylformamide.

"DMSO" means dimethylsulfoxide.

"DOI" means (±)-1-(2,5-dimethoxy-4-[^{125}I]-iodophenyl)-2-aminopropane.

"EDC" means 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride.

"EDTA" means ethylenediaminetetraacetic acid.

"EE" means energy expenditure.

"EtOAc" means ethyl acetate.

"GC-MS" means gas chromatography – mass spectrometry.

"GDP" means guanosine diphosphate.

"GTP" means guanosine triphosphate.

"GTPγ[^{35}S]" means guanosine triphosphate having the terminal phosphate substituted with ^{35}S in place of an oxygen.

"HATU" means O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate.

"HMPA" means hexamethylphosphoramide.

"HOBT" means 1-hydroxybenzotriazole hydrate.

"HPLC" means high-pressure liquid chromatography.

"HRMS" means high-resolution mass spectrometry.

"ISPA" means immunoadsorption scintillation proximity assay.

"*m*-CPBA" means *meta*-chloroperoxybenzoic acid.

"mp" means melting point.

"Ms" in a chemical structure means the methanesulfonyl moiety (-SO_2CH_3).

"MS (ES+)" means mass spectroscopy using electrospray ionization.

"MTBE" means methyl *t*-butyl ether.

"NBS" means *N*-bromosuccinimide.

"NMP" means 1-methyl-2-pyrrolidinone.

"NMR" means nuclear magnetic resonance.

"Pd/C" means palladium on activated carbon.

"RQ" means respiratory quotient.

"SCX chromatography" means chromatography on an SCX column or cartridge.

"SCX column" or "SCX cartridge", as used herein, refers to a Varian Bond Elute® silica based strong cation exchange resin column or disposable cartridge or equivalent.

"Sudan III" means 1- [(4-phenylazo)phenylazo]-2-naphthalenol.

"Tf" in a chemical structure means the trifluoromethanesulfonyl moiety ($-SO_2CF_3$).

"TFA" means trifluoroacetic acid.

"THF" means tetrahydrofuran.

"TLC" means thin layer chromatography.

While all of the compounds of the present invention are useful as 5-HT_{2C} agonists, certain classes are preferred, as for example, compounds having any of the following enumerated selections of substituents: Compounds wherein

1) R^7 is halo;
2) R^7 is chloro;
3) R^7 is $(C_1–C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents;
4) R^7 is $(C_1–C_3)$alkyl optionally substituted with 1 to 6 fluoro substituents;
5) R^7 is $–CF_3$;
6) R^7 is $(C_3–C_6)$alkenyl optionally substituted with 1 to 6 fluoro substituents;
7) R^7 is $(C_3–C_6)$alkenyl;
8) R^7 is cyano;
9) R^{1-5} are each hydrogen;
10) R^4 is methyl or ethyl;
11) R^4 is methyl;
12) R^3 is methyl;
13) R^8 is hydrogen;
14) R^9 is $(C_1–C_3)$alkoxy;
15) R^9 is methoxy;
16) R^9 is halo;
17) R^9 is chloro;
18) R^6 is $–C\equiv C-R^{10}$;
19) R^{10} is $Ph^1-(C_0–C_3)$alkyl;
20) R^{10} is $Ph^1-(C_1–C_2)$alkyl;

21) R^{10} is Phenyl(C_0–C_3)alkyl;

22) R^{10} is (C_3–C_7)cycloalkyl(C_0–C_3)alkyl;

23) R^{10} is (C_3–C_7)cycloalkylmethyl;

24) R^{10} is (C_4–C_6)alkyl;

25) R^{10} is branched (C_4–C_6)alkyl;

26) R^{10} is (C_1–C_6)alkyl substituted with 2-6 fluoro substituents;

27) R^{10} is Ar^1-(C_0–C_3)alkyl;

28) R^{10} is Ar^1-(C_1–C_2)alkyl;

29) R^6 is –O-R^{12};

30) R^{12} is Ph^2-(C_0–C_3)alkyl;

31) R^{12} is Ph^2-(C_1–C_2)alkyl;

32) R^{12} is Ph^2-(C_1–C_2)alkyl and Ph^2 is substituted with 1-3 halo substituents;

33) R^{12} is Ph^2-(C_1–C_2)alkyl and Ph^2 is substituted with 1-3 fluoro substituents;

34) R^{12} is Ph^2-(C_1–C_2)alkyl and Ph^2 is substituted with cyano;

35) R^{12} is Ph^2-(C_1–C_2)alkyl and Ph^2 is substituted with $R^{30}R^{31}$N-S(O)$_2$-;

36) R^{12} is Ph^2-(C_1–C_2)alkyl, Ph^2 is substituted with $R^{30}R^{31}$N-S(O)$_2$-, R^{30} is (C_1-C_3)alkyl optionally further substituted with 1-3 fluoro substituents and R^{31} is hydrogen;

37) R^{12} is Ar^2-(C_0–C_3)alkyl;

38) R^{12} is Ar^2-(C_1–C_2)alkyl;

39) R^{12} is Ar^2-(C_1–C_2)alkyl and Ar^2 is pyridyl, thiazolyl, oxazolyl, or pyrazolyl, each optionally substituted with methyl;

40) R^{12} is benzazolyl-(C_1–C_3)alkyl;

41) R^{12} is Ph^2-C(O)-(C_1–C_3)alkyl,

42) R^{12} is Ph^2-C(O)-(C_1–C_3)alkyl and Ph^2 is substituted with 1 to 3 halo substituents;

43) R^{12} is Ph^2-C(O)-(C_1–C_3)alkyl and Ph^2 is substituted with 1 to 3 halofluoro substituents;

44) R^{12} is Ph^1-S(O)$_2$–;

45) R^{12} is (C_1–C_6)alkyl-O-C(O)-(C_3–C_6)alkyl;

46) R^{12} is (C_1–C_3)alkyl-O-C(O)-(C_3–C_6)alkyl;

47) R^{12} is R^{13}-C(O)NH-(C_2–C_4)alkyl;

48) R^{12} is R^{13}-C(O)NH-(C_2–C_4)alkyl and R^{13} is Ph^1;

49) R^{12} is R^{13}-C(O)NH-(C_2–C_4)alkyl, R^{13} is Ph^1; substituted with 1 to 3 halo substituents;

50) R^{12} is R^{13}-C(O)NH-(C_2–C_4)alkyl and R^{13} is (C_3–C_7)cycloalkyl;

51) R^{12} is R^{13}-C(O)NH-(C_2–C_4)alkyl and R^{13} is pyridyl;

52) R^{12} is R^{13}-C(O)NH-(C_2–C_4)alkyl and R^{13} is (C_1–C_3)alkoxy;

53) R^{12} is R^{13}-C(O)NH-(C_2–C_4)alkyl and R^{13} is (C_3–C_7)cycloalkyl;

54) R^6 is –S-R^{14};

55) R^6 is –S-R^{14} and R^{14} is Ph^2;

56) R^6 is –S-R^{14}, R^{14} is Ph^2 substituted with 1 to 3 halo substituents;

57) R^6 is –S-R^{14}, R^{14} is Ph^2 substituted with cyano;

58) R^6 is –S-R^{14}, R^{14} is Ph^2; substituted with cyano and 1 to 2 halo substituents;

59) R^6 is –S-R^{14} and R^{14} is Ar^2;

60) R^6 is –S-R^{14}, R^{14} is Ar^2, and Ar^2 is optionally substituted pyridyl or pyridazinyl;

61) R^6 is –S-R^{14}, R^{14} is Ar^2, and Ar^2 is optionally substituted thiophenyl, thiazolyl, isothiazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl;

62) R^6 is –S-R^{14} and R^{14} is tetrahydrofuranyl or tetrahydropyranyl;

63) R^6 is –S-R^{14} and R^{14} is tetrahydrofuranyl or tetrahydropyranyl and the tetrahydrofuranyl or tetrahydropyranyl is substituted with oxo on a carbon adjacent to the ring oxygen;

64) R^6 is –S-R^{14} and R^{14} is R^{15}-L-;

65) L is (C_1–C_2)alkylene;

66) L is branched (C_2–C_3)alkylene;

67) L is methyl-methylene;

68) L is di-methyl-methylene;

69) L is methyl-ethylene;

70) L is gem-di-methyl-ethylene;

71) L is gem-ethano-ethylene;

72) R^{15} is Ph^2;

73) R^{15} is Ph^2 substituted with 1 to 3 halo substituents;

74) R^{15} is Ph^2 substituted with cyano;

75) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkoxy;

76) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkoxy optionally further substituted with 1 to 3 fluoro substituents;

77) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkoxy$(C_1–C_1)$alkyl;

78) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkoxy$(C_1–C_1)$alkyl further substituted with 1 to 3 fluoro substituents;

79) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkylthio;

80) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkylthio optionally further substituted with 1 to 3 fluoro substituents;

81) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkylthio$(C_1–C_1)$alkyl;

82) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkylthio$(C_1–C_1)$alkyl further substituted with 1 to 3 fluoro substituents;

83) R^{15} is Ph^2 substituted with $(C_3–C_7)$cycloalkyl$(C_0–C_1)$alkyl;

84) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkylsulfonyl$(C_0–C_1)$alkyl optionally further substituted with 1 to 3 fluoro substituents;

85) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkylsulfinyl$(C_0–C_1)$alkyl optionally further substituted with 1 to 3 fluoro substituents;

86) R^{15} is Ph^2 substituted with Ph^1-$(C_0–C_1)$alkyl-sulfonyl;

87) R^{15} is Ph^2 substituted with Ph^1-$(C_0–C_1)$alkyl;

88) R^{15} is Ph^2 substituted with $R^{26}R^{27}N$-;

89) R^{15} is Ph^2 substituted with Het^1;

90) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkyl-C(O)- optionally further substituted with 1 to 3 fluoro substituents;

91) R^{15} is Ph^2 substituted with $(C_1–C_6)$alkyl—O-C(O)- optionally further substituted with 1 to 3 fluoro substituents;

92) R^{15} is Ph^2 substituted with Ph^1;

93) R^{15} is Ph^2 substituted with $Ph^1(C_0–C_3)$alkyl-O-;

94) R^{15} is Ph^2 substituted with $Ph^1(C_0–C_3)$alkyl-C(O)-;

95) R^{15} is Ph^2 substituted with $Ph^1(C_0–C_3)$alkyl-C(O)-;

96) R^{15} is Ph^2 substituted with $Ar^2(C_0–C_3)$alkyl-C(O)-;

97) R^{15} is Ph^2 substituted with $Ar^2(C_0–C_3)$alkyl-C(O)- and Ar^2 is pyrazolyl optionally further substituted as provided for in Ar^2;

98) R^{15} is Ph^2 substituted with $R^{28}R^{29}N$-C(O)-;

99) R^{15} is Ph^2 substituted with $R^{28}R^{29}N$-C(O)- and R^{28} is $(C_1–C_6)$alkyl;

100) R^{15} is Ph^2 substituted with $R^{28}R^{29}N$-C(O)- and R^{28} is $(C_3$-$C_7)$cycloalkyl$(C_0$-$C_3)$alkyl;

101) R^{15} is Ph^2 substituted with $R^{28}R^{29}N$-C(O)- and R^{28} is Ph^1-$(C_0$-$C_2)$-*n*-alkyl optionally substituted on the alkyl moiety when present with $(C_1$-$C_3)$alkyl, dimethyl, or gem-ethano;

102) R^{15} is Ph^2 substituted with $R^{28}R^{29}N$-C(O)- and R^{28} is Ar^2-$(C_0$-$C_2)$-*n*-alkyl optionally substituted on the alkyl moiety when present with $(C_1$-$C_3)$alkyl, dimethyl, or gem-ethano;

103) R^{15} is Ph^2 substituted with Het^1-C(O)-;

104) R^{15} is Ph^2 substituted with Het^1-C(O)- further substituted with Ph^1;

105) R^{15} is Ar^2;

106) R^{15} is Ar^2 further substituted with methyl;

107) R^{15} is Ar^2 further substituted with $(C_3–C_7)$cycloalkyl$(C_0–C_2)$alkyl, Het^1, pyridyl, or phenyl optionally further substituted with methyl, $-CF_3$, cyano, $-SCF_3$, or with 1 to 3 halo substituents;

108) R^{15} is pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, furanyl, oxazolyl, isoxazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, thiophenyl, thiazolyl, isothiazolyl, 1,2,3-thiadiazolyl, or 1,3,4-thiadiazolyl, any of which may optionally be substituted with 1 to 3 substituents selected from the group consisting of halo, cyano, $–SCF_3$, $(C_1$-$C_6)$alkyl optionally further substituted with 1 to 6 fluoro, and $(C_1$-$C_6)$alkoxy optionally further substituted with 1 to 6 fluoro.

109) R^{15} is pyridyl optionally further substituted as provided for in Ar^2;

110) R^{15} is tetrahydrofuranyl or tetrahydropyranyl, either optionally being substituted with an oxo substituent, or with one or two groups selected independently from methyl and $–CF_3$;

111) R^{15} is tetrahydrofuranyl or tetrahydropyranyl, being substituted with an oxo substituent, and optionally being further substituted with one or two groups selected independently from methyl and $–CF_3$;

112) R^{15}–L- is pyrid-2-yl-methyl;

113) R^{15}–L- is pyrid-3-yl-methyl;

114) R^{15}–L- is pyrid-2-yl-$CH(CH_3)$-;

115) R^{15}–L- is pyrid-3-yl-$CH(CH_3)$-;

116) R^{15} is pyridazinyl optionally further substituted as provided for in Ar^2;

117) R^{15}–L- is pyridazin-2-yl-methyl;

118) R^{15}–L- is pyridazin-3-yl-methyl;

119) R^{15}–L- is pyridazin-2-yl-$CH(CH_3)$-;

120) R^{15}–L- is pyridazin-3-yl-$CH(CH_3)$-;

121) R^{15} is pyridyl further substituted with $(C_3–C_7)$cycloalkyl$(C_0–C_2)$alkyl, Het^1, pyridyl, or phenyl optionally further substituted with methyl, $-CF_3$, cyano, $-SCF_3$, or with 1 to 3 halo substituents;

122) R^{15} is pyridazinyl further substituted with $(C_3–C_7)$cycloalkyl$(C_0–C_2)$alkyl, Het^1, pyridyl, or phenyl optionally further substituted with methyl, $-CF_3$, cyano, $–SCF_3$, or with 1 to 3 halo substituents;

123) R^{15} is R^{22}-C(O)-;

124) R^{15} is R^{22}-C(O)- and R^{22} is $(C_1$-$C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents;

125) R^{15} is R^{22}-C(O)- and R^{22} is $(C_1$-$C_6)$alkoxy optionally substituted with 1 to 6 fluoro substituents;

126) R^{15} is R^{22}-C(O)- and R^{22} is $(C_3$-$C_7)$cycloalkyl$(C_0$-$C_3)$alkyl;

127) R^{15} is R^{22}-C(O)- and R^{22} is $(C_3$-$C_7)$cycloalkyl$(C_0$-$C_3)$alkyl-O-;

128) R^{15} is R^{22}-C(O)- and R^{22} is Ph^1-$(C_0$-$C_3)$alkyl;

129) R^{15} is R^{22}-C(O)- and R^{22} is Ph^1-$(C_0$-$C_3)$alkyl-O-;

130) R^{15} is R^{22}-C(O)- and R^{22} is Ar^2-$(C_0$-$C_3)$alkyl;

131) R^{15} is R^{22}-C(O)- and R^{22} is Ar^2-$(C_0$-$C_3)$alkyl-O-;

132) R^{15} is R^{22}-C(O)- and R^{22} is $R^{32}R^{33}N$-;

133) R^{15} is phthalimido;

134) R^{15} is $R^{17}R^{18}N$-;

135) R^{15} is $R^{17}R^{18}N$- and R^{17} is $(C_1$-$C_3)$alkoxy-C(O)-;

136) R^{15} is $R^{17}R^{18}N$- and R^{17} is $(C_3$-$C_7)$cycloalkyl$(C_0$-$C_2)$-C(O)-;

137) R^{15} is $R^{17}R^{18}N$- and R^{17} is Ph^1-$(C_0$-$C_2)$-C(O)-;

138) R^{15} is $R^{17}R^{18}N$- and R^{17} is Ar^2-$(C_0$-$C_2)$-C(O)-;

139) R^{15} is $R^{16}O$-;

140) R^{15} is $R^{16}O$- and R^{16} is $(C_1\text{-}C_6)$oalkyl-C(O)-;

141) R^{15} is $R^{16}O$- and R^{16} is $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_2)$-C(O)-;

142) R^6 is $R^{24}R^{25}N$- and R^{24} is $(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_5)$alkyl optionally substituted with 1 to 6 fluoro substituents;

143) R^6 is $R^{24}R^{25}N$- and R^{24} is $(C_1\text{-}C_6)$alkylthio$(C_2\text{-}C_5)$alkyl optionally substituted with 1 to 6 fluoro substituents;

144) R^6 is $R^{24}R^{25}N$- and R^{24} is $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_1)$alkyl-O-$(C_1\text{-}C_5)$alkyl;

145) R^6 is $R^{24}R^{25}N$- and R^{24} is $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_1)$alkyl-S-$(C_1\text{-}C_5)$alkyl;

146) R^6 is $R^{24}R^{25}N$- and R^{24} is phenyl$(C_1\text{-}C_3)$ *n*-alkyl optionally substituted on the *n*-alkyl moiety when present with $(C_1\text{-}C_3)$alkyl, dimethyl, or gem-ethano;

147) R^6 is $R^{24}R^{25}N$- and R^{24} is Ph^2-$(C_1\text{-}C_3)$ *n*-alkyl optionally substituted on the *n*-alkyl moiety when present with $(C_1\text{-}C_3)$alkyl, dimethyl, or gem-ethano;

148) R^6 is $R^{24}R^{25}N$- and R^{24} is $Ar^2(C_0\text{-}C_3)$ *n*-alkyl optionally substituted on the *n*-alkyl moiety when present with $(C_1\text{-}C_3)$alkyl, dimethyl, or gem-ethano;

149) R^6 is $R^{24}R^{25}N$- and R^{24} is $Ar^2(C_0\text{-}C_3)$ *n*-alkyl optionally substituted on the *n*-alkyl moiety when present with $(C_1\text{-}C_3)$alkyl, dimethyl, or gem-ethano, wherein Ar^2 contains a nitrogen atom, and Ar^2 is substituted;

150) R^6 is $R^{24}R^{25}N$- and R^{24} is $Ar^2(C_0\text{-}C_3)$ *n*-alkyl optionally substituted on the *n*-alkyl moiety when present with $(C_1\text{-}C_3)$alkyl, dimethyl, or gem-ethano, wherein Ar^2 contains a nitrogen atom, and Ar^2 is substituted with $(C_1\text{-}C_6)$alkoxy optionally further substituted with 1 to 6 fluoro, $(C_1\text{-}C_6)$alkylamino optionally further substituted with 1 to 6 fluoro, or $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_2)$alkyl optionally further substituted with 1 to 6 fluoro;

151) R^6 is $R^{24}R^{25}N$- and R^{24} is $Ar^2(C_0\text{-}C_3)$ *n*-alkyl optionally substituted on the *n*-alkyl moiety when present with $(C_1\text{-}C_3)$alkyl, dimethyl, or gem-ethano, and wherein Ar^2 is pyridyl or pyridazinyl and is substituted with $(C_1\text{-}C_6)$alkoxy optionally further substituted with 1 to 6 fluoro, $(C_1\text{-}C_6)$alkylamino optionally further substituted with 1 to 6 fluoro, or $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_2)$alkyl optionally further substituted with 1 to 6 fluoro;

152) R^6 is $R^{24}R^{25}N$- and R^{24} is $Ar^2(C_0\text{-}C_3)$ *n*–alkyl optionally substituted on the *n*-alkyl moiety when present with $(C_1\text{-}C_3)$alkyl, dimethyl, or gem-ethano, and wherein Ar^2 is pyridyl substituted with $R^{28}R^{29}N$-C(O)- and R^{28} is $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_2)$alkyl or Ph^1 and R^{29} is hydrogen;

153) R^6 is $R^{24}R^{25}N$- and R^{24} is $Ar^2(C_0\text{-}C_3)$ *n*–alkyl, wherein Ar^2 is pyridyl substituted with $R^{28}R^{29}N$-C(O)- and R^{28} is $(C_3\text{-}C_7)$cycloalkyl or phenyl optionally substituted with 1 to 3 halo, preferably fluoro, and R^{29} is hydrogen;

154) R^6 is $R^{24}R^{25}N$- and R^{24} is Ph^1-$(C_0\text{-}C_1)$alkyl-O-$(C_1\text{-}C_5)$alkyl;

155) R^6 is $R^{24}R^{25}N$- and R^{24} is Ph^1-$(C_0\text{-}C_1)$alkyl-S-$(C_1\text{-}C_5)$alkyl;

156) R^6 is $R^{24}R^{25}N$- and R^{24} is Ph^1-$(C_0\text{-}C_1)$alkyl-C(O)NH-$(C_2\text{-}C_4)$alkyl;

157) R^6 is $R^{24}R^{25}N$- and R^{24} is Ph^1-$(C_0\text{-}C_1)$alkyl-NH-C(O)NH-$(C_2\text{-}C_4)$alkyl;

158) R^6 is $R^{24}R^{25}N$- and R^{24} is pyridyl-$(C_0\text{-}C_1)$alkyl-C(O)NH-$(C_2\text{-}C_4)$alkyl optionally substituted on the pyridyl moiety with methyl, $-CF_3$, or 1 to 3 halo substituents;

159) R^6 is $R^{24}R^{25}N$- and R^{24} is pyridyl-$(C_0\text{-}C_1)$alkyl-NH-C(O)NH-$(C_2\text{-}C_4)$alkyl optionally substituted on the pyridyl moiety with methyl, $-CF_3$, or 1 to 3 halo substituents;

160) R^6 is $R^{24}R^{25}N$- and R^{24} is Ar^3-$(C_1\text{-}C_2)$alkyl;

161) R^6 is $R^{24}R^{25}N$- and R^{24} is Ar^3-methyl;

It will be understood that the above classes may be combined to form additional preferred classes. Exemplary combinations include, but are not limited to:

162) Any one of preferred embodiments 19) through 161) (the preferred selections for R^6), combined with any one of preferred embodiments 1) through 9) (the preferred selections for R^7);

163) Any one of preferred embodiments 19) through 161) (the preferred selections for R^6), wherein R^7 is halogen;

164) Any one of preferred embodiments 19) through 161) (the preferred selections for R^6), wherein R^7 is chloro;

165) A preferred combination according to 162), 163), or 164), wherein $R^{1\text{-}5}$, and R^8 are each hydrogen;

166) A preferred combination according to 162), 163), or 164), wherein R^{1-5}, R^8 and R^9, are each hydrogen.

167) Any one of preferred embodiments 37), 38), or 39), wherein R^7 is other than hydrogen;

168) Any one of preferred embodiments 37), 38), or 39), wherein R^9 is hydrogen;

169) Any one of preferred embodiments 37), 38), or 39), wherein R^7 is other than hydrogen and R^9 is hydrogen;

170) Any one of preferred embodiments 37), 38), or 39), wherein R^7 is chloro and R^9 is hydrogen;

171) compounds of formula (I) wherein R^6 is $-C{=}C-R^{10}$ and wherein R^{10} is selected from the values defined in any one of embodiments 19) to 28);

172) compounds of formula (I) wherein R^6 is $-O-R^{12}$ and wherein R^{12} is selected from the values defined in any one of embodiments 30) to 53);

173) compounds of formula (I) wherein R^6 is -S-R^{14} and wherein R^{14} is selected from the values defined in any one of embodiments 55) to 63) or 64) wherein L is selected from the values of 65) to 71) and R^{15} is selected from the values defined in any one of embodiments 72) to 141);

174) compounds of formula (I) wherein R^6 is $R^{24}R^{25}N$- and wherein R^{24} is selected from the values defined in any one of embodiments 142) to 161);

175) compounds according to embodiment 172) wherein R^{12} is selected from the values defined in any one of embodiments 37), 38) or 39);

176) compounds of formula (I) wherein R^7 is other than hydrogen;

177) compounds according to any one of embodiments 171) or 174) wherein R^7 is other than hydrogen;

178) compounds according to any one of embodiments 171) or 174) wherein R^7 is choro;

179) compounds according to any one of embodiments 171) or 174) wherein R^9 is hydrogen;

180) compounds according to any one of embodiments 171) or 174) wherein R^9 is $(C_1–C_3)$alkoxy;

181) compounds according to any one of embodiments 171) or 174) wherein R^9 is methoxy;

182) compounds according to any one of embodiments 171) or 174) wherein R^7 is choro and R^9 is hydrogen;

183) compounds according to any one of embodiments 171) or 174) wherein R^7 is choro and R^9 is (C_1–C_3)alkoxy;

184) compounds according to any one of embodiments 171) or 174) wherein R^7 is choro and R^9 is methoxy;

185) compounds according to any one of embodiments 171) or 185) wherein R^9 is hydrogen;

186) compounds according to any one of embodiments 171) or 185) wherein R^9 is (C_1–C_3)alkoxy;

187) compounds according to any one of embodiments 171) or 185) wherein R^9 is methoxy;

188) compounds according to any one of embodiments 171) or 187) wherein $R^{1\text{-}5}$ are each hydrogen;

Generally, when R^6 is –S-R^{14}, then R^{15}-L- is the more preferred R^{14}. When R^{14} or R^{15} is substituted Ar^2, para-substitution is preferred. When L is present, particularly preferred are methylene, and methyl-methylene. Particularly preferred R^{15}-L- is when R^{15} is Ph^2 and L is methylene. Also particularly preferred is when R^{15} is Ph^2 and L is methyl-methylene. Also particularly preferred is when R^{15} is Ar^2 and L is methylene. Also particularly preferred is when R^{15} is Ar^2 and L is methyl-methylene.

Also generally, when R^6 is -$NR^{24}R^{25}$, then Ph^2-(C_1-C_3)-*n*-alkyl is particularly preferred over phenyl(C_1-C_3)-*n*-alkyl.

Preferred compounds of formula (I) are those wherein

R^6 is –C≡C-R^{10} and wherein R^{10} is selected from the values defined in any one of embodiments 19) to 28); or

R^6 is –O-R^{12} and wherein R^{12} is selected from the values defined in any one of embodiments 30) to 53); or

R^6 is -S-R^{14} and wherein R^{14} is selected from the values defined in any one of embodiments 55) to 63) or embodiment 64) wherein L is selected from

the values defined in any one of embodiments 65) to 71) and R^{15} is selected from the values defined in any one of embodiments 72) to 111) and 121 to 141), or R^{15}-L- is selected from the values defined in any one of embodiments 112) to 120); or

R^6 is $R^{24}R^{25}N$- and wherein R^{24} is selected from the values defined in any one of embodiments 143) to 161).

Particularly preferred compounds of formula (I) are those wherein R^6 is –O-R^{12} and wherein R^{12} is selected from the values defined in any one of embodiments 37), 38) or 39).

Further preferred compounds of formula (I) are those wherein R^7 is other than hydrogen. In particular, R^7 is preferably selected from the values defined in any one of embodiments 1) to 8). More preferably, R^7 is selected from halo (especially chloro), (C_1-C_3)alkyl optionally substituted with 1 to 6 fluoro substituents (especially methyl, ethyl, *n*-propyl or CF_3), and cyano.

Particularly preferred compounds of formula (I) are those wherein R^7 is halogen, and in particular wherein R^7 is chloro.

Preferred compounds of formula (I) are those wherein R^9 is (C_1-C_3)alkoxy, preferably methoxy, or halo, preferably chloro.

Also preferred are those compounds of formula (I) wherein R^9 is hydrogen.

Particularly preferred compounds of formula (I) are those wherein R^7 is other than hydrogen and R^9 is hydrogen, and most especially wherein R^7 is chloro and R^9 is hydrogen.

Further preferred compounds of formula (I) are those wherein R^1 is hydrogen.

Also preferred are those compounds of formula (I) wherein R^2 is hydrogen.

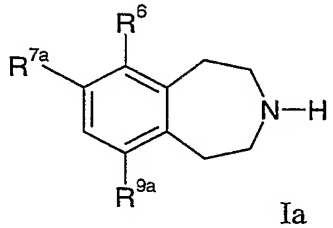
Also preferred are those compounds of formula (I) wherein R^3 is hydrogen or methyl, and especially wherein R^3 is hydrogen.

Another preferred class of compounds of formula (I) is that wherein R^4 is hydrogen, methyl or ethyl, particularly wherein R^4 is hydrogen or methyl, and especially wherein R^4 is hydrogen.

Further preferred are those compounds of formula wherein R^5 is hydrogen.

Also preferred are those compounds of formula (I) wherein R^8 is hydrogen.

One favored group of compounds of the present invention is that represented by formula (Ia), and pharmaceutically acceptable salts thereof:



Ia

wherein

R^{7a} is halogen, and especially chloro;

R^{9a} is hydrogen, halogen or (C_1-C_3)alkoxy, particularly hydrogen, chloro or methoxy, and especially hydrogen; and

R^6 is as defined in relation to formula (I).

Specific preferred compounds of the present invention are those described in the Examples herein, including the free bases and the pharmaceutically acceptable salts thereof.

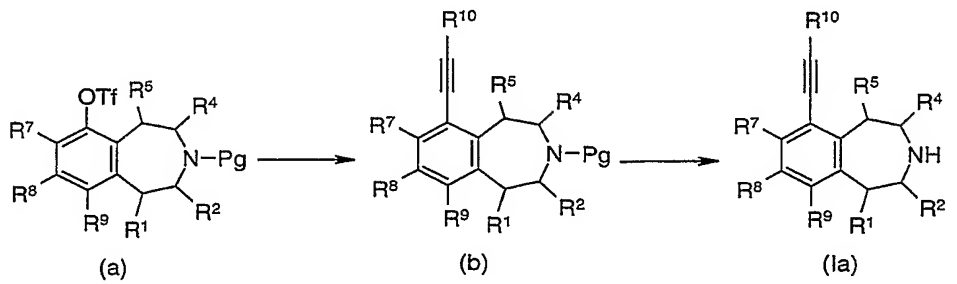
It will be appreciated that the preferred definitions of the various substituents recited herein may be taken alone or in combination and, unless otherwise stated, apply to

the generic formula (I) for compounds of the present invention, as well as to the preferred class of compounds represented by formula (Ia).

The compounds of the invention can be prepared according to the following synthetic schemes by methods well known and appreciated in the art. Suitable reaction conditions for the steps of these schemes are well known in the art and appropriate substitutions of solvents and co-reagents are within the skill of the art. Likewise, it will be appreciated by those skilled in the art that synthetic intermediates may by isolated and/or purified by various well known techniques as needed or desired, and that frequently, it will be possible to use various intermediates directly in subsequent synthetic steps with little or no purification. Furthermore, the skilled artisan will appreciate that in some circumstances, the order in which moieties are introduced is not critical. The particular order of steps required to produce the compounds of Formula I is dependent upon the particular compound being synthesized, the starting compound, and the relative liability of the substituted moieties as is well appreciated by those of ordinary skill in the art. All substituents, unless otherwise indicated, are as previously defined, and all reagents are well known and appreciated in the art.

Compounds of Formula I where R^6 is an acetylene-linked substituent may be prepared as illustrated in Scheme I where Pg is a suitable protecting group for a secondary amine such as, but not limited to, 2,2,2-trifluoroacetyl or *tert*-butoxycarbonyl, and variables R^1, R^2, R^4, R^5, R^7, R^8, R^9 and R^{10} are as previously defined.

Scheme I



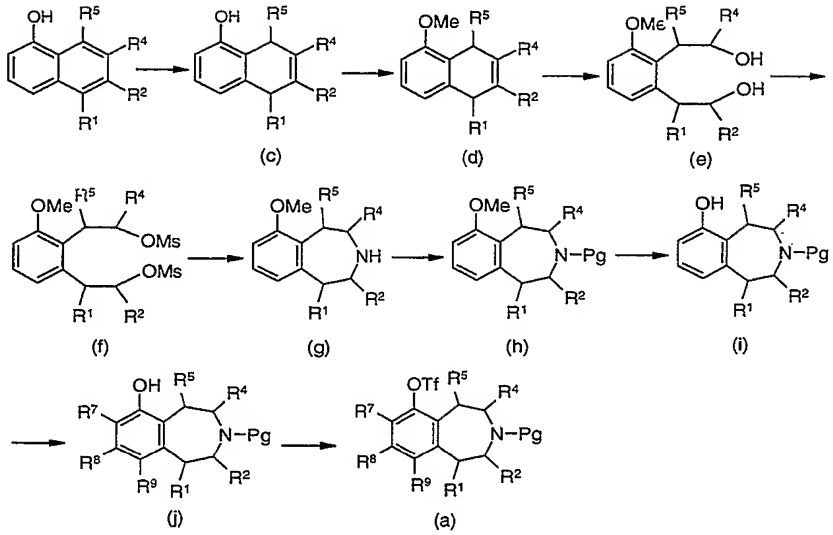
Mix the 6-triflate of the 2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepines (a) with an appropriately substituted acetylene, a suitable palladium/copper catalyst mixture in a

solvent, typically DMF, using triethylamine as base, and heat to afford the desired compound (b). Deprotection reaction and the standard extractive and chromatographic techniques afford the desired compound (Ia).

The appropriate 6-triflate of 2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepines (a) may be prepared as described in Scheme II. Compound (a) may be prepared from 1-naphthol. 1-Naphthol can be converted to 5-hydroxy-1,4-dihydronaphthalene (c) by Birch reduction using ammonia and lithium metal at low temperature. Methylation of the 6-hydroxy group affords the compound (d). Ozonolysis of (d) and subsequent reduction with sodium borohydride provide the diol (e). After converting the two hydroxyl groups into two good leaving groups, for example methanesulfonates, cyclize the compound (f) to the 6-methoxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepines (g) with aqueous ammonia under pressure. Protect the ring nitrogen with a variety of alkyl halides, acid chlorides or anhydrides such as trifluoroacetic anhydride to give compound (h). Subsequently convert the methyl ether (h) to the phenol (i) with BBr_3 in dichloromethane or other methods well known in the literature [see for example, Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley and sons, Chapter III, New York (1999)].

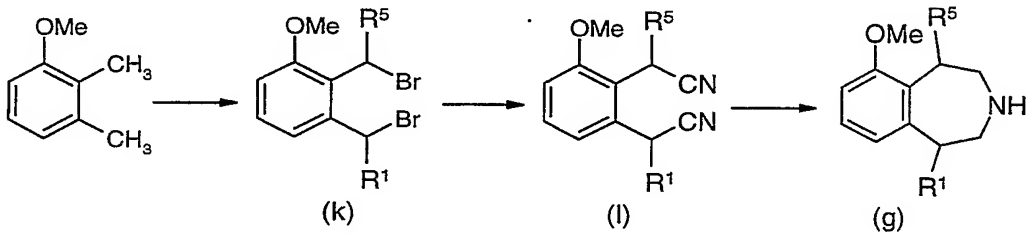
Functionalization of the aromatic ring to introduce substituents R^7, R^8 and R^9 are well known in the art and very depending on the substitution desired. Subsequent trifluoromethanesulfonylation of the 6-hydroxy (j) affords the desired 2,3,4,5-tetrahydro-*1H*-benzo[d]azepines (a).

Scheme II



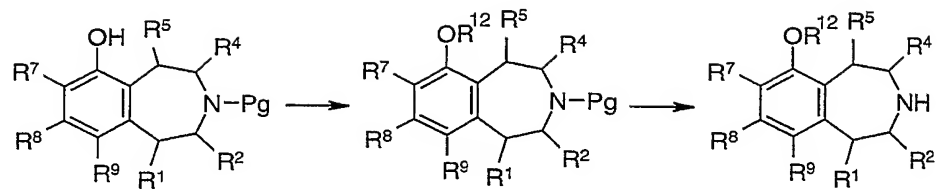
Alternately, compound (g) could be prepared from 1,2-bis(cyanomethyl)-3-methoxybenzene (l), previously described in the literature (*J. Med. Chem.* 1984, 27, 918-921), as shown in Scheme III below.

Scheme III



Compounds of Formula I where R^6 is an oxygen-linked substituent may be prepared as illustrated in Scheme IV where Pg is a suitable protecting group for secondary amine, such as 2,2,2-trifluoroacetyl or tert-butoxycarbonyl, and variables R^7, R^9 and R^{12} are as previously defined.

Scheme IV



(j) (m) (Ib)

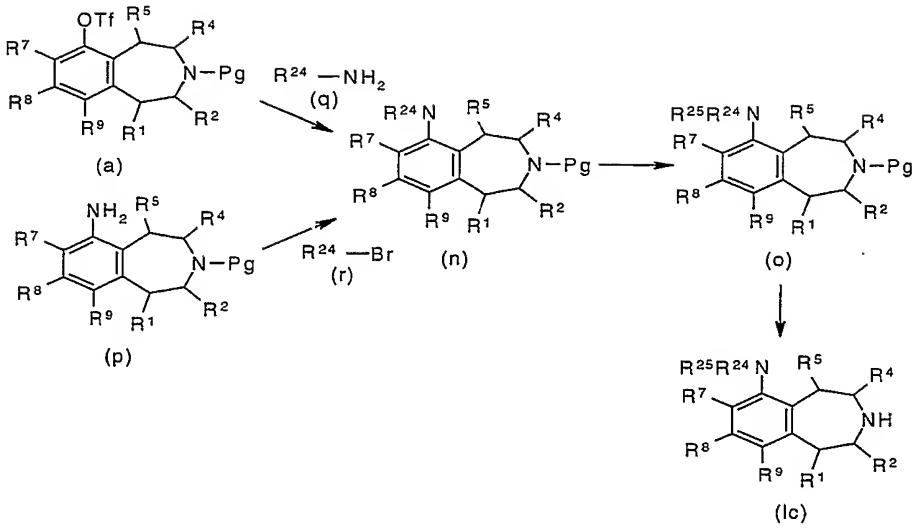
Compound (m) can be prepared by treating 6-hydroxy-2,3,4,5-tetrahydro-*1H*-benzo[d]azepines (j) with an appropriate alkylation reagent, such as an alkyl halide or sulfonate, and a base in a suitable solvent, typically acetone, ethanol or acetonitrile, followed by he standard extractive and chromatographic techniques. Deprotection of the ring nitrogen gives the compound (Ib). Alternately, compound (m) can be obtained by Mitsunobu reaction with an appropriate alcohol, a phosphine reagent such as triphenylphosphine, and diethyl azodicarboxylate (DEAD) or 1,1'-(azodicarbonyl)-dipiperidine in an anhydrous solvent, for example THF.

Compounds of Formula Ic where R^6 is a nitrogen-linked substituent may be prepared as illustrated in the Scheme V. The 6-triflate protected 2,3,4,5-tetrahydro-*1H*-benzo[d]azepines (a) can be converted to the compounds (n), under Buchwald conditions, by treatment with an appropriate amine (q) in the presence of an effective palladium catalyst, and a base in a suitable solvent, typically toluene or 1,4-dioxane under an inert atmosphere. Introduction of a second substituent R^{25}, if needed, may be performed. Standard work-up and chromatographic techniques followed by deprotection, give the compound (Ic).

Alternately 6-amino-2,3,4,5-tetrahydro-*1H*-benzo[d]azepines (p) can be transformed to the desired compounds (n) by reaction with an appropriate bromide (r), and an appropriate base in a suitable solvent.

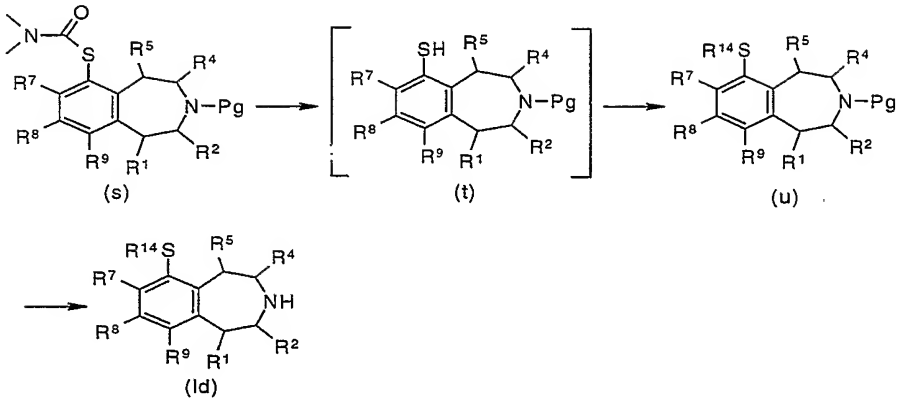
Bromides (r) are either commercially available or may be prepared by methods well known to the skilled artisan. Amines (q) are either commercially available or may be prepared by methods well known to the skilled artisan.

Scheme V



Compounds of Formula I where the R^6 is a sulfur-linked substituent may be prepared as illustrated in the Scheme VI.

Scheme VI



Heat the appropriately substituted 3-(tert-butoxycarbonyl-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine (s) with an appropriate base in a suitable solvent, such as methanol, to obtain the intermediate thiol (t). Isolate the intermediate thiol (t), if required, and treat it with an appropriate electrophile (halide or alkyl sulfonate). Isolate the compound (u) by standard extractive and chromatographic techniques and deprotect to afford the desired compound (Id).

The requisite halides or alkyl sulfonates are either commercially available or may be prepared by methods well known to the skilled artisan.

The skilled artisan will also appreciate that not all of the substituents in the compounds of Formula I will tolerate certain reaction conditions employed to synthesize the compounds. These moieties may be introduced at a convenient point in the synthesis, or may be protected and then deprotected as necessary or desired, as is well known in the art. The skilled artisan will appreciate that the protecting groups may be removed at any convenient point in the synthesis of the compounds of the present invention. Methods for introducing and removing protecting groups used in this invention are well known in the art; see, for example, Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley and sons, New York (1999).

The following Preparations and Examples are illustrative of methods useful for the synthesis of the compounds of the present invention. Exemplified compounds are also particularly preferred compounds of the present invention.

General Procedure 1-1

Dissolve the appropriately substituted 3-(2,2,2- trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine in ammonia/methanol solution (1.0–7.0 M). Stir for 1-16 h at ambient temperature unless otherwise specified. Remove the volatiles *in vacuo*. Purify by chromatography on silica gel eluting with 1-20% 2M ammonia/methanol in DCM, or by SCX chromatography eluting with 1.0-7.0 M ammonia in methanol.

General Procedure 1-2

Dissolve the appropriately substituted 3-(2,2,2- trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.0 equiv.) in methanol. Add a 0.5 M aqueous solution of potassium carbonate (4.0 equiv.) and stir at ambient temperature for 6 h. Concentrate *in vacuo* and partition the residue between water and DCM. Extract the aqueous phase twice with DCM. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. If needed, purify by chromatography on silica gel eluting with 1-20% 2M ammonia/methanol in DCM, or by SCX chromatography eluting with 1.0-7.0 M ammonia in methanol.

General Procedure 1-3

Dissolve the appropriately substituted 3-(2,2,2- trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.0 equiv.) in methanol or ethanol (0.1 to 2M solution) and add from 10-50% by volume of a 1.0-5.0 N aqueous solution of sodium hydroxide or lithium hydroxide. Stir the reaction mixture at ambient temperature for 0.25-16 h and concentrate *in vacuo*. Partition the residue between EtOAc or DCM and water. Separate and dry the organic fraction over Na_2SO_4, filter, and concentrate *in vacuo*. Purify by SCX chromatography, followed by chromatography on silica gel eluting with 1-20% 2M ammonia/methanol in DCM or reverse phase HPLC.

General Procedure 1-4

Dissolve the appropriately substituted 3-*tert*-butoxycarbonyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine in 4M hydrogen chloride in dioxane or 1M hydrogen chloride in ethyl ether and stir the mixture for 2-16 h at ambient temperature unless otherwise specified. Remove the solvent *in vacuo*. If a solid is obtained, wash the solid with ether and filter under vacuum to afford the desired hydrochloride salt. If an oil is obtained, dissolve the oil in the minimal volume of DCM, methanol or EtOAc and add ether to precipitate out the solid. Remove the solvent *in vacuo*, wash the solid with ether and filter. Dry the solid *in vacuo* or under a stream of nitrogen.

General Procedure 1-5

Dissolve the appropriately substituted 3-*tert*-butoxycarbonyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine in a mixture of trifluoroacetic acid/DCM (from 1:0 to 1:10 ratio) and stir the reaction for 1-16 h at ambient temperature. Concentrate *in vacuo* and either subject the residue to SCX chromatography or partition the residue between saturated aqueous $NaHCO_3$ and DCM or EtOAc. Dry the organic layer over Na_2SO_4 and concentrate *in vacuo*. Purify by either chromatography on silica gel (eluting with 1-20% 2M ammonia/methanol in DCM) or reverse phase HPLC.

General Procedure 1-6

Add acetyl chloride (40 equiv.) to cold methanol (0 °C) and stir for 5 min. Then add a solution of the appropriately substituted 7-chloro-3-(*tert*-butoxycarbonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1 equiv.) in methanol. Stir the reaction at ambient temperature for 12 h. Remove the solvent *in vacuo*, basify with saturated aqueous $NaHCO_3$ and extract three times with DCM. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel, eluting with 1-20% 2M ammonia/methanol in DCM.

General Procedure 2-1

Dissolve the purified free base (1 equiv.) in acetone, ether or methanol and add a solution of succinic acid (1 equiv.) in a minimal volume of acetone or methanol. Stir for 1 h at ambient temperature. Concentrate to an oil, add a minimal volume of DCM and

ethyl ether to precipitate out the salt. Alternatively, to precipitate out the salt, allow the reaction mixture to stand 1-16 h at ambient temperature, 4 °C or –10 °C and add ether or hexane. Filter and wash the solid with ether or hexane to obtain the succinate salt. Alternatively, evaporate the solvent *in vacuo*, wash the solid with ether and filter or decant the solvent to obtain the succinate as a solid. Dry the solid *in vacuo* or under a stream of nitrogen.

General Procedure 2-2

Dissolve the purified free base (1 equiv.) in a minimal volume of acetone, dioxane, methanol or DCM and add an excess of 4M hydrogen chloride in dioxane or a 1M solution of hydrogen chloride in ethyl ether. Stir for 1 h and evaporate the solvent to obtain the salt as a solid. Alternatively, allow the reaction mixture to stand 1 to 16 h at ambient temperature and add ether or hexane to precipitate out the salt. Filter and wash the solid with ether or hexane to obtain the salt as a solid. Alternatively, evaporate the solvent *in vacuo*, wash the solid with ether, filter or decant the solvent to obtain the hydrochloride salt as a solid. Dry the solid *in vacuo* or under a stream of nitrogen.

General Procedure 2-3

Dissolve the purified free base in methanol, add a solution of ammonium chloride (1 equiv.) in methanol and stir for 1 h. Slowly remove the volatiles *in vacuo*. Dissolve the residue in methanol and remove most of the solvent *in vacuo*. Add anhydrous ethyl ether or EtOAc to precipitate out the hydrochloride salt. Collect the solid, wash the solid with ether and then dry the solid *in vacuo* or under a stream of nitrogen.

General Procedure 2-4

Dissolve the purified free base (1.0 equiv.) in methanol. Add a 0.5 M solution of methanesulfonic acid in methanol (2.0 equiv). Mix well, stir for 1 h, then remove the solvent *in vacuo*. Dissolve the residue into a minimal volume of DCM. Add ethyl ether to precipitate out the solid. Remove the solvent *in vacuo* to form a foam. Dry *in vacuo* or under a stream of nitrogen to obtain the methanosulfonic acid salt.

General Procedure 2-5

Dissolve the purified free base (1 equiv.) in a minimal volume of acetone and add a solution of oxalic acid (1 equiv.) in a minimal volume of acetone. Allow the mixture to stand 10 min to 16 h at ambient temperature to -10°C, and/or add ether or hexane to precipitate out the solid. Filter and wash the solid with ether or hexane to obtain the oxalic acid salt as a solid. Dry the solid *in vacuo* or under a stream of nitrogen.

General Procedure 2-6

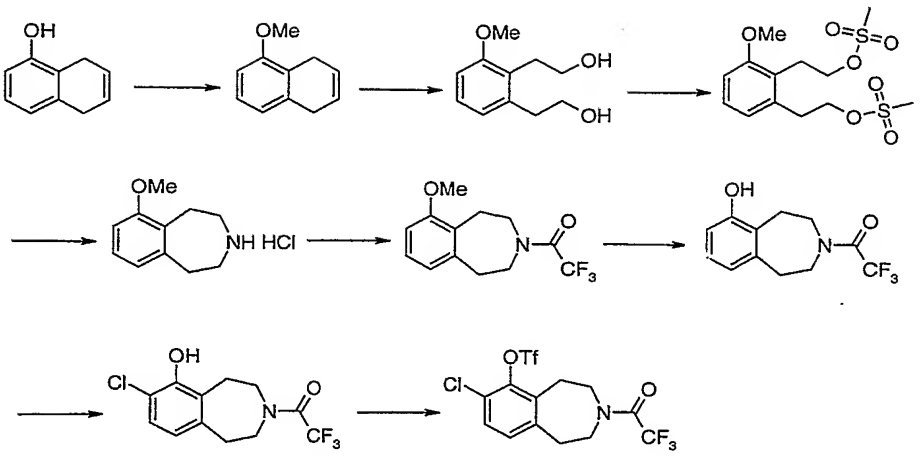
Dissolve the purified free base (1 equiv.) in a minimal volume of cyclohexane, isohexane, chloroform, dichloromethane, methanol or a mixture thereof and add a solution of (*L*)-tartaric acid in isopropanol or methanol. If a solid precipitate out, filter and wash the solid with ether, cyclohexane, isohexane or EtOAc. If no solid formation is observed, remove all the volatiles *in vacuo* to form a foam. Dry *in vacuo* or under a stream of nitrogen to obtain the tartaric acid salt.

General Procedure 3

Dissolve the appropriately substituted 3-*tert*-butoxycarbonyl-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine or 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1 equiv.), $PdCl_2(PPh_3)_2$ (0.1 equiv.), tetrabutyl ammonium iodide (3 equiv.), and copper(I) iodide (0.3 equiv.) in triethylamine/DMF (1:5). Stir the mixture for 5 min at ambient temperature, add the appropriately substituted acetylene (2 equiv.) and heat at 70 °C for 2-16 h in a sealed tube. Cool the reaction mixture to ambient temperature, dilute with EtOAc/hexane (1:1) and wash with water. Dry the organic fraction over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc mixtures.

Preparation 1

7-Chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



5-Methoxy-1,4-dihydronaphthalene: Add powdered potassium carbonate (193.1 g, 1.397 mol) to a solution of 5-hydroxy-1,4-dihydronaphthalene [68.08 g, 90% potency based on ^{1}H-NMR, 0.4657 mol, from Societa Italiana Medicinala Scandicci, s.r.l., Reggello (Firenze), Italy] in ethanol (700 mL). Cool the solution to 0°C with ice/water and add dimethyl sulfate (88.1 g, 66.1 mL, 0.699 mol) dropwise, maintaining the temperature between 5°C and 10°C. Then heat the reaction mixture to 40°C until the TLC (10:1 hexane/EtOAc) shows the absence of starting material (about 2 h). Filter off the solids by vacuum filtration and remove the solvent *in vacuo*. Dilute the residual brown oil with diethyl ether (500 mL), wash with 10% aqueous NH_4OH (500 mL), water (500 mL), brine (500 mL), dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo* to give the crude product as a brown oil (73 g). Purify the crude product by short path distillation under vacuum (bp 120-130°C/ 5 Torr) to give the desired intermediate as a clear oil (69.0 g, 92.5% potency corrected) (contains some 1,2,3,4-tetrahydro-5-methoxynaphthalene as an impurity). ^{1}H NMR (300 MHz, $CDCl_3$), δ7.15 (t, 1H, J = 7.9), 6.72 (dd, 2H, J = 15.7, 7.9), 5.93-5.88 (m, 2H), 3.83 (s, 3H), 3.42-3.39 (m, 2H), 3.30-3.28 (m, 2 H); R_f = 0.58 eluting with 10:1 hexane/EtOAc.

2,3-Bis-(2-hydroxyethyl)-1-methoxybenzene: Charge a four-neck 5 L flask equipped with an over-head mechanical stirrer, reflux condenser, thermocouple, and gas dispersion apparatus with 5-methoxy-1,4-dihydronaphthalene (264.54 g, 89.5% potency based on ^{1}H-NMR, 1.478 mol) in DCM (1.3 L) and 2B-3 ethanol (1 L). Add sudan III (10 mg) to give a faint red color. Cool the solution to -65°C or lower, then pass O_3 through the

solution until the solution turns a light yellow color and the TLC (10:1 hexane/EtOAc, $KMnO_4$ stain) shows the absence of the starting material (about 30 h). Transfer the solution via cannula into a slurry of $NaBH_4$ (97.8 g, 2.59 mol) in 2B-3 ethanol (500 mL) cooled in ice/water. It is important that the temperature be maintained at or above 0°C, as for example between 0°C and 10°C, throughout the transfer to ensure the ozonide is completely reduced to the diol. After the transfer is complete, warm the solution to ambient temperature and stir for about 30 min. Cool the slurry to 0°C with ice/water then slowly add acetone (540 mL, 7.4 mol) to remove excess $NaBH_4$. After all the solids dissolve, remove the solvent *in vacuo*. Dissolve the yellow solid in DCM (1 L) and water (1 L), separate the layers and extract the aqueous layer with DCM (750 mL). Wash the combined organic layers with brine (1.5 L), add toluene (750 mL) and remove the solvent *in vacuo*. Dissolve the solid in DCM (500 mL) with heating, then add toluene (750 mL) and concentrate the solution *in vacuo* to give the desired intermediate as a light yellow solid (283.7 g, 89% potency corrected, mp 82-83°C) (contains 1,2,3,4-tetrahydro-5-methoxynaphthalene as an impurity (8.6%)). Further purify the product by vacuum drying overnight at 75°C, 5 Torr, to remove all but trace amount of the 1,2,3,4-tetrahydro-5-methoxynaphthalene impurity. ^1H NMR (300 MHz, $CDCl_3$), δ 7.16 (dd, 1H, J = 8.2, 7.6), 6.83 (s, 1H, J = 7.0), 6.76 (s, 1H, J = 8.2), 3.85-3.77 (m, 7H), 3.01-2.91 (m, 4H), 2.35 (s, 2H); ^{13}C NMR (300 MHz, DMSO-d_6), δ 157.5, 138.9, 126.5, 125.2, 122.0, 108.4, 62.1, 60.5, 55.3, 36.1, 29.6; IR (KBr): 3006, 2960, 2886, 2829, 1583, 1461, 1440, 1264, 1091, 1041 cm^{-1}; MS (ES+) *m/z* 178 $(M+H)^+$; Anal. Calc'd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22; N, 0. Found: C, 67.26, H, 8.10, N, 0.21; R_f = 0.23 eluting with 95:5 DCM/methanol.

2,3-Bis-(2-methanesulfonyloxyethyl)-1-methoxybenzene: To a slurry of 2,3-bis-(2-hydroxyethyl)-1-methoxybenzene (50.6 g, 0.258 mol, 1 equiv.) and triethylamine (78.3 g, 0.774 mol, 3 equiv.) in DCM (500 mL) at 0°C, add dropwise a solution of methanesulfonyl chloride (65.0 g, 0.567 mol, 2.2 equiv.) in DCM (100 mL) over 45 min. The addition is exothermic and the methanesulfonyl chloride is added at a rate to keep the temperature below 10°C. After the addition is complete, warm the reaction to ambient temperature. Wash the solution with water (2 x 500 mL), and then brine (750 mL). Dry

the organic layer over Na_2SO_4, filter and concentrate *in vacuo* to obtain the desired intermediate as a dark yellow oil (87.4 g, 96.2%), which is used in the next reaction without further purification. An analytical sample is obtained by flash column chromatography eluting with 100% diethyl ether. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.20 (t, 1H, J = 7.9), 6.82 (s, 1H, J = 7.2), 6.80 (s, 1H, J = 8.2), 4.41-4.34 (m, 4H), 3.83 (s, 3H), 3.16-3.09 (m, 4H), 2.91 (s, 3H), 2.87 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$), δ 158.07, 136.55, 128.26, 123.34, 122.39, 109.24, 69.88, 69.08, 55.55, 37.35, 37.14, 32.57, 26.47; ^{13}C NMR (300 MHz, DMSO-d_6), δ 157.58, 136.79, 127.81, 122.91, 122.00, 109.33, 70.19, 68.88, 55.55, 36.49, 36.47, 31.56, 25.72; IR (KBr): 1586.8, 1469.4, 1358.51, 1267.3, 1173.9, 1105.4, 972.4, 954.6, 914.3 cm^{-1}; MS (ES+) *m/z* 257 $(M+H)^+$; Anal. Calc'd. for $C_{13}H_{20}O_7S_2$: C, 44.31; H, 5.72; N, 0. Found: C, 44.22, H, 5.68, N, 0.13; R_f = 0.72 eluting with 95:5 DCM/methanol.

6-Methoxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 2,3-bis-(2-methanesulfonyloxyethyl)-1-methoxybenzene (474.4 g, 1.346 mol) in acetonitrile (7 L) and split the mixture into two equal lots. In two separate runs, add concentrated aqueous NH_4OH (3.5 L) and charge the solution to a pressure vessel (PARR apparatus). Heat the solution in a closed reactor to 100°C over 20 min (internal pressure reaches about 100 psi), and maintain at 100°C until the reaction is complete (about 1 h, HPLC monitored). Cool the reaction mixture to ambient temperature. Combine the two lots and remove the solvent *in vacuo*. Dissolve the residue in MTBE (3.5 L) and water (3.5 L). Adjust the pH to 6.5 using 2M aqueous NaOH or 1M aqueous HCl as appropriate (typically the pH is about pH=5.1 and the adjustment requires about 50 mL 2M aqueous NaOH). Discard the organic layer, adjust the aqueous layer to pH=13 using 50% NaOH (about 150 mL). Extract with MTBE (2 x 3.5 L), wash the combined organic layers with brine (3.5 L), dry over Na_2SO_4, filter and concentrate *in vacuo* to give the title compound as a crude yellow oil that solidifies upon standing (179.3 g). Use the material for the next step without further purification. Prepare an analytical sample by purification by two Kugelrohr distillations to give a clear oil that solidifies upon standing, mp 44.3-45.0°C. ^{13}C NMR (300 MHz, DMSO-d_6) □ 156.1, 144.4, 130.3, 126.2, 121.5, 108.9, 55.5, 48.2, 47.9, 39.9,

29.1; MS (ES+) *m/z* 163 $(M+H)^+$; Anal. Calc'd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.28, H, 8.62, N, 7.86.

6-Methoxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride: Dissolve crude 6-methoxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (35.1 g, 0.198 mol) in 2B-3 ethanol (250 mL), heat the solution to reflux and add 2M HCl in ethanol (108.9 mL, 0.218 mol, 1.1 equiv.). Slowly add heptane (700 mL) over 10 min, then remove the heating mantle and cool the solution to ambient temperature, and finally continue the cooling with an ice/water mixture. Collect the resulting solid by vacuum filtration and wash with cold ethanol:heptane (1:2) (3 x 100 mL), air-dry for 15 min under vacuum, then further dry the product in a vacuum oven at 60°C for 1 h to give the desired intermediate as a white granular solid (35.53 g, 63%): mp 246.6-246.9°C; ^{1}H NMR (300 MHz, DMSO-d_6), δ 9.82 (broad s, 1H), 7.12 (dd, 1H, J = 7.6, 7.9), 6.88 (d, 1H J = 8.2), 6.78 (d, 1H, J = 7.3), 3.75 (s, 3H), 3.20-3.00 (m, 8H); ^{13}C NMR (300 MHz, DMSO-d_6), δ 156.2, 141.3, 127.4, 127.2, 121.6, 109.7, 55.7, 44.9, 44.7, 31.6, 21.7; MS (ES+) *m/z* 178 $(M+H)^+$; Anal. Calc'd for $C_{11}H_{15}ClNO$: C, 62.12; H, 7.11; N, 6.59. Found: C, 61.95, H, 7.64, N, 6.58.

6-Methoxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: To a slurry of 6-methoxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine hydrochloride (35.3 g, 0.165 mol, 1 equiv.) and triethylamine (69.1 mL, 0.496 mol, 3 equiv.) in DCM (300 mL) cooled at 0°C with ice/water, add dropwise a solution of trifluoroacetic anhydride (25.7 mL, 0.182 mol, 1.1 equiv.) in DCM (40 mL) over 30 min, but at a rate that maintains the temperature below 10°C. After the addition is complete, warm the reaction mixture to ambient temperature and stir until the reaction is complete (verify by TLC using 9:1 CH_2Cl_2:methanol, about 2 h.). Wash the solution with water (2 x 350 mL), and then brine (350 mL), dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo* to give desired intermediate as a yellow oil that solidifies upon standing (44.9 g, 96%). Use the material without further purification in the next step. Prepare an analytical sample by chromatography on silica gel eluting with 40% diethyl ether in hexane, mp 74-76°C. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.16-7.11 (m, 1H), 6.81-6.74 (m, 2H), 3.81 (s, 3H), 3.79-3.64 (m, 4H), 3.11-3.07 (m, 2H), 2.99-2.95 (m, 2H); ^{1}H NMR (300 MHz, DMSO-d_6), δ 7.13

(dd, 1H, J = 1.5, 7.0), 7.08 (d, 1H, J = 1.5), 6.88-6.74 (m, 1H), 3.75 (s, 3H), 3.67-3.61 (m, 4H), 3.04-2.92 (m, 4H); ^{13}C NMR (300 MHz, DMSO-d_6), δ 156.43. 156.38, 155.06, 155.00, 154.60, 154.54, 154.14, 154.08, 141.31, 141.04, 127.44, 127.18, 127.05, 127.01, 122.27, 121.94, 121.90, 118.46, 114.64, 110.80, 109.52, 109.41, 55.63, 55.61, 47.11, 47.07, 46.67, 46.63, 45.61, 45.16, 35.90, 34.65, 26.18, 24.91; Anal. Calc'd for $C_{13}H_{14}F_3NO_2$: C, 57.14; H, 5.16; N, 5.13. Found: C, 57.17, H, 5.27, N, 5.08.

6-Hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: To a 1M solution of BBr_3 (1.1 L, 1.6 equiv.), cooled at 0°C with an ice-water bath, add 6-methoxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (187 g, 0.684 mol) in DCM (200 mL) over 1 h., while maintaining the temperature between 0°C and 10°C. Warm the reaction mixture to ambient temperature and stir until HPLC indicates completion of the reaction (about 2 h.). Cool the solution to 0°C and transfer it via cannula into an ice/water solution (1.2 L), thereby precipitating the product as a white solid. Add EtOAc (2 L) to dissolve most of the precipitate, separate the layers and concentrate the organic layer *in vacuo*. Extract the aqueous layer three times with EtOAc (2 x 2 L, 1 x 1 L). Wash the combined organic layers with water (2 L), and then brine (2 L), dry over Na_2SO_4, filter and concentrate *in vacuo* to give the desired intermediate as a light yellow solid (166.3 g, 94%). Use the product for the next step without further purification. Prepare an analytical sample by chromatography on silica gel eluting with 40% diethyl ether in hexane: mp 183.0-185.2°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ 9.39 (s, 1H), 6.94-6.88 (m, 1H), 6.72-6.68 (m, 1H), 6.61-6.57 (m, 1H), 3.67-3.32 (m, 4H), 2.99-2.86 (m, 4H); ^{13}C NMR (300 MHz, DMSO-d_6), δ 154.50, 141.47, 141.18, 126.77, 126.64, 125.77, 125.33, 120.38, 120.32, 118.49, 114.67, 113.64, 113.47, 47.31, 47.27, 47.00, 46.96, 45.83, 45.49, 36.17, 34.93, 26.46, 25.18, 20.66, 14.00; MS (ES+) *m/z* 260 $(M+H)^+$; Anal. Calc'd. for $C_{12}H_{12}F_3NO_2$: C, 55.60; H, 4.67; N, 5.40. Found: C, 55.51, H, 4.71, N, 5.29.

7-Chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Heat a mixture of 6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (120 g, 0.4629 mol) and toluene (14.4 L) to 70°C for 45 min until most

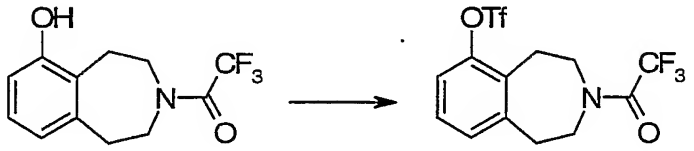
of the starting material is dissolved. Add diisobutylamine (1.197 g, 1.62 mL, 9.26 mmol) followed by addition of sulfuryl chloride (62.48 g, 37.19 mL, 0.463 mol) in toluene (360 mL) over 20 min. Stir the reaction mixture for 50 min and then add additional sulfuryl chloride (4.536 g, 2.70 mL, 0.0336 mol) neat and stir the reaction mixture for 15 min at 70°C. Cool the reaction mixture to 24°C over 30 min and then add 1N hydrochloric acid (2.00 L). Separate, wash the organic layer with saturated aqueous $NaHCO_3$ (2.00 L), brine (2.00 L) and then dry over Na2SO4. Filter and remove the solvent with a rotary evaporator at 70°C until about 672.5 g remains using the minimum effective vacuum in order to maintain a vapor phase sufficient to prevent drying above the solvent line and self-seeding, thus preventing crystallization under these conditions. Using toluene heated to 70°C, transfer the light-yellow solution to a preheated (70°C) 3-neck flask equipped with a mechanical stirrer. Lower the temperature to 58°C over 1 h. If available, seed the solution with crystals of 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine from a prior synthesis to enhance crystallization. After 30 min, reduce the temperature further to 55°C and observe the initiation of the crystallization process. Hold the temperature at 55°C for 2 h. followed by 4 h. at 45°C, then turn off the heat allowing the mixture to slowly reach 24°C (ambient temperature). After stirring for 8 h. with the heat off, cool the mixture to 0°C for 2 h. followed by 2 h. at -10°C. Collect the resulting dense, white, granular crystals by vacuum filtration at -10°C. Rinse the crystals twice with cold (-10°C) toluene and vacuum dry at 50°C, 5 Torr, for 12 h., to obtain the desired intermediate as a white solid (120.7 g, 99.5% purity, 88.8%): mp 133-134°C. MS (ES+) *m/z* 294 $(M+H)^+$. Anal. Calc'd for $C_{12}H_{11}ClF_3NO_2$: C, 49.08; H, 3.78; N, 4.77; Cl, 12.07. Found: C, 49.01; H, 3.63; N, 4.72; Cl, 12.32.

7-Chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Cool a solution of 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (60 g, 0.204 mol), triethylamine (62.6 mL, 0.448 mol, 2.2 equiv.), and DCM (590 mL) in an ice bath and add dropwise trifluoromethanesulfonic anhydride (43.5 mL, 0.258 mol, 1.26 equiv.) over 70 min. Remove the ice bath and stir the reaction mixture for 2 h. Wash the reaction mixture sequentially with water (500 mL), 1N aqueous HCl (500 mL), water (500 mL), and brine (500 mL). Dry the organic layer over Na_2SO_4 and concentrate *in vacuo* to give the crude

product as a brown solid (90 g). Dissolve the solid in warm toluene (200 mL). Further purify by plug filtration chromatography over silica gel (500 g) eluting sequentially with hexane (1 L), hexane/EtOAc (9:1, 1L), hexane/EtOAc (4:1, 1L), and hexane/EtOAc (7:3, 9L). Pool the eluents and evaporate the solvent to obtain the product as a yellow tan solid (86.3 g). Dissolve the solid in warm EtOAc (86 mL) and then add hexane (700 mL). If available, seed the solution with crystals of 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanelsulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine from a prior synthesis to enhance crystallization. Allow the mixture to stand at ambient temperature for 30 min. Cool the mixture at about -10°C for 2 h., filter, rinse the crystals with cold (-10°C) hexane/EtOAc, and air-dry on the filter under vacuum to obtain the title compound as a first crop of crystals (73.54 g). Concentrate the mother liquor to obtain a solid (12.7 g). Recrystallize the solid in a mixture of EtOAc/hexane (15 mL:121 mL) to obtain additional title compound (7.65 g, total yield: 81.19 g, 93%).

Preparation 2

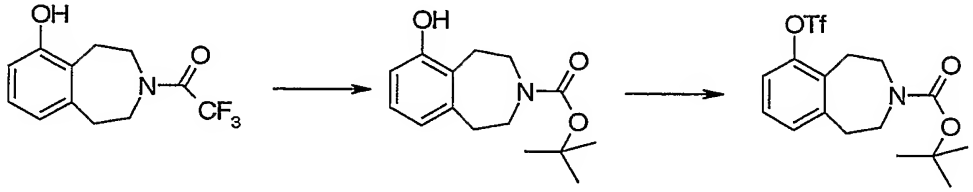
3-(2,2,2-Trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



Cool a solution of 6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2 g, 7.72 mmol), triethylamine (1.4 mL, 10.1 mmol) and DCM (50 mL) in a cryogenic bath set at –30 °C and add dropwise trifluoromethanesulfonic anhydride (1.7 mL, 10.1 mmol) over 20 min. Stir at –30°C for 2 h and then warm to ambient temperature overnight. Wash the reaction mixture sequentially with water (100 mL), 1N aqueous HCl (100 mL), water (200 mL), and brine (200 mL). Dry the organic layer over Na_2SO_4 and concentrate *in vacuo* to give the title compound as a colorless to light yellow oil (2.7 g, 89%) that was used without purification. Obtain an analytical sample by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the title compound as an off-white waxy solid. GC-MS *m/z*: 391 (M^+).

Preparation 3

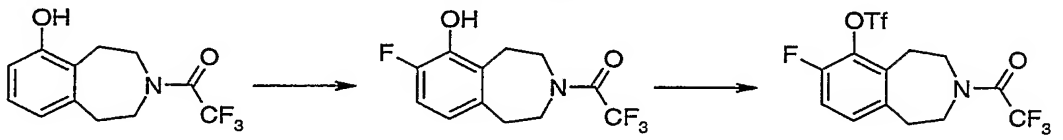
3-*tert*-Butoxycarbonyl-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



Dissolve 6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (5 g, 19.3 mmol) in 7N ammonia in methanol (50 mL) and stir at ambient temperature for 16 h. Concentrate the reaction mixture to an oil and use without further purification. Dissolve the residue in a solvent mixture consisting of methanol (20 mL), DCM (10 mL) and water (100 mL), and add potassium carbonate (5 g) and di-*tert*-butyl-dicarbonate (5.05 g, 23.2 mmol). Stir the reaction mixture at ambient temperature for 16 h and concentrate *in vacuo*. Extract the aqueous phase with DCM, dry over Na_2SO_4, filter and concentrate. Use the residue without further purification. Dissolve the material in a mixture of DCM (300 mL) and pyridine (30 mL) and cool in an ice bath. Add dropwise to the stirred solution trifluoromethanesulfonic anhydride (5.84 mL, 34.7 mmol) and stir the reaction mixture for 2 h at ambient temperature. Dilute the reaction mixture with DCM (400 mL) and wash with 2.5N aqueous HCl. Dry the organic fraction over Na_2SO_4, filter and concentrate to give the title compound as a yellow solid (6.1 g, 80%). MS (ES+) *m/z*: 396 $(M+H)^+$.

Preparation 4

7-Fluoro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

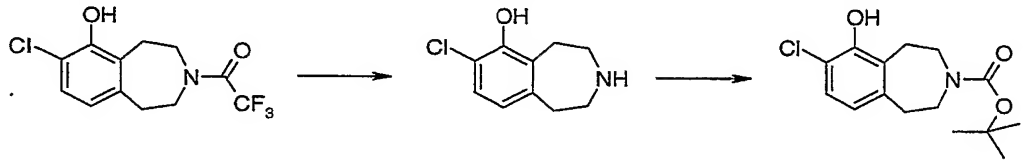


Add *N*-fluoro-4,6-bis(trifluoromethyl)-pyridinium 2-sulfonate (3.02 g, 9.6 mmol) to a stirred mixture of 6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2.5 g, 9.6 mmol) and hexafluoro-2-propanol (10 mL) in DCM (150

mL). Stir at ambient temperature for 16 h. Concentrate the reaction mixture and partition the residue between EtOAc and 1N aqueous HCl. Wash the organic fraction with saturated aqueous $NaHCO_3$, brine, dry over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (20:1, 10:1, 6:1, 5:1 and 3:1) to give 7-fluoro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a white solid (1.8 g, 68%). Dissolve 7-fluoro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.5 g, 5.41 mmol) in a mixture of DCM (20 mL) and pyridine (2 mL) and cool in an ice bath. Add dropwise to the stirred solution a mixture of trifluoromethanesulfonic anhydride (1.64 mL, 9.74 mmol) in DCM and stir the reaction for 1.5 h at ambient temperature. Dilute the reaction with DCM (300 mL) and wash with 2.5N aqueous HCl. Dry the organic fraction over Na_2SO_4, filter and concentrate to give the title product as a white solid (2.2 g, 99%). MS (ES+) *m/z*: 410 $(M+H)^+$.

Preparation 5

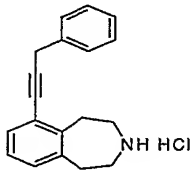
3-*tert*-Butoxycarbonyl-7-chloro-6-hydroxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



Dissolve 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (3 g, 10.2 mmol) in 7 N ammonia in methanol (50 mL) and stir at ambient temperature for 16 h. Concentrate the reaction mixture to an oil and use without further purification. Dissolve the residue in a solvent mixture consisting of DCM (25 mL) and saturated aqueous potassium carbonate solution (25 mL) and add di-*tert*-butyl-dicarbonate (2.2 g, 10.2 mmol). Stir the reaction mixture at ambient temperature for 4 h, concentrate *in vacuo* and extract the aqueous residue with DCM. Dry the organic fraction over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:5) to give the title compound as a white solid (2.3 g, 76%). MS (ES-) *m/z*: 296 $(M-H)^-$.

Example 1

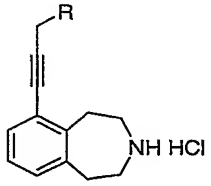
6-(3-Phenyl-prop-1-ynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the General Procedure 3 to couple 3-*tert*-butoxycarbonyl-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.6 g, 1.5 mmol) with 3-phenyl-1-propyne (0.38 mL, 3 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 40:1 and 20:1) to give 3-*tert*-butoxycarbonyl-6-(3-phenyl-prop-1-ynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an orange oil (400 mg, 74%).

Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-6-(3-phenyl-prop-1-ynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (68 mg, 0.19 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (1:0, 20:1 and 10:1) to obtain the free base of the title compound. Use a method similar to the General Procedure 2-2 to give the title compound as a tan solid (48 mg, 85%). MS (ES+) *m/z*: 262 $(M+H)^+$.

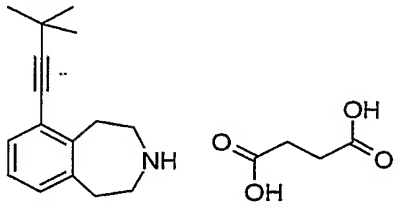
Examples 2–4 may be prepared essentially as described in Example 1 by using 3-*tert*-butoxycarbonyl-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate alkyne. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	R	Compound	Yield (%)	MS (ES+) *m/z*
2	Benzyl	6-(4-Phenyl-but-1-ynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	60	276 $(M+H)^+$
3	Cyclopentyl	6-(3-Cyclopentyl-prop-1-ynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	73	254 $(M+H)^+$
4	Cyclohexyl	6-(3-Cyclohexyl-prop-1-ynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	79	268 $(M+H)^+$

Example 5

6-(3,3-Dimethyl-but-1-ynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

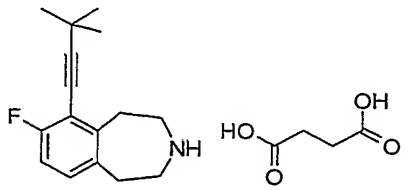


Use a method similar to the General Procedure 3 to couple 3-*tert*-butoxycarbonyl-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.5 g, 1.3 mmol) with 3,3-dimethyl-1-butyne (0.311 mL, 2.5 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1) to give 3-*tert*-butoxycarbonyl-6-(3,3-dimethyl-but-1-ynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (304 mg, 74%).

Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-6-(3,3-dimethyl-but-1-ynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (1:0, 50:1, 20:1, 15:1 and 10:1) to obtain the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound as a tan solid (171 mg, 53%). MS (ES+) *m/z*: 228 $(M+H)^+$.

Example 6

6-(3,3-Dimethyl-but-1-ynyl)-7-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the General Procedure 3 to couple 7-fluoro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1 g, 2.4 mmol) with 3,3-dimethyl-1-butyne (0.599 mL, 4.9 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1) to give 6-(3,3-dimethyl-but-1-ynyl)-7-fluoro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (700 mg, 84%).

Use a method similar to the General Procedure 1-3 to deprotect 6-(3,3-dimethyl-but-1-ynyl)-7-fluoro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by SCX chromatography followed by chromatography on silica gel eluting with DCM/2M ammonia in methanol (1:0, 50:1, 20:1, 15:1 and 10:1) to obtain the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound as a white solid (589 mg, 83%). MS (ES+) *m/z*: 246 $(M+H)^+$.

General Procedure 4-1

Add 7-chloro-6-hydroxy-3-(2,2,2–trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1 equiv.), the appropriate alkylating agent (1.2 equiv.), ground K_2CO_3 (3 equiv.) and KI (0.1 equiv.) to a proper solvent (acetone, ethanol or acetonitrile) and heat to reflux for 6 to 16 h unless otherwise specified. Cool the reaction mixture to ambient temperature, quench with 1N aqueous HCl and extract the aqueous layer three times with EtOAc. Combine the organic fractions, wash with saturated aqueous $NaHCO_3$, brine, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc mixtures.

General Procedure 4-2

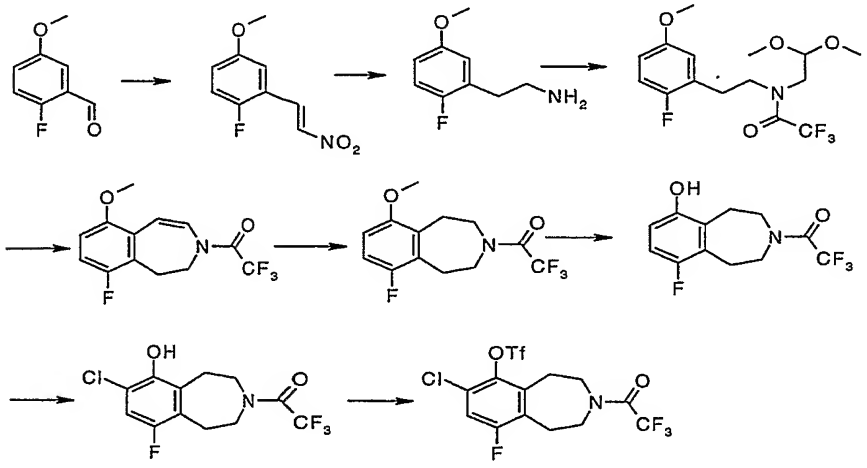
Add 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1 equiv.), the appropriate alcohol (1.1 equiv.), triphenylphosphine (1.2 equiv.) and diethyl azodicarboxylate (1.1 equiv.) sequentially to anhydrous THF. Stir the mixture at ambient temperature under nitrogen. Re-add triphenylphosphine (1.2 equiv.) and diethyl azodicarboxylate (1.1 equiv.) if the reaction is not completed (monitored by TLC). Dilute the mixture with EtOAc, wash with saturated aqueous $NaHCO_3$, brine, dry over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc mixtures.

General Procedure 4-3

Add 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1 equiv.), the appropriate alcohol (1.2-1.5 equiv.) and triphenylphosphine (1.5 equiv.) sequentially to anhydrous THF. Stir the mixture at 0°C under nitrogen for 10 min. Add 1,1'-(azodicarbonyl)dipiperidine (1.5 equiv.) and let the mixture warm to ambient temperature over 16 h. Dilute with ether, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc mixtures.

Preparation 6

7-Chloro-9-fluoro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



1-Fluoro-4-methoxy-2-(2-nitro-vinyl)-benzene: Heat 2-fluoro-5-methoxybenzaldehyde (15 g, 97.4 mmol) with nitromethane (32 mL, 584 mmol) and ammonium acetate (30 g, 390 mmol) in acetic acid (136 mL) under reflux for 30 min. Evaporate the solvent and dissolve the residue in ether. Wash the organic fraction with water, saturated aqueous $NaHCO_3$ and evaporate to give the desired intermediate (18.7 g, 97%). GC-MS *m/z*: 197 $(M)^+$.

2-(2-Fluoro-5-methoxyphenyl)-ethylamine: Cautiously add sulfuric acid (14.7 mL, 265 mmol) dropwise at 0°C to lithium aluminum hydride (1M solution in THF, 565 mL) with efficient stirring. Warm the mixture to ambient temperature for 20 min and then cool back to 0°C. Add a solution of 1-fluoro-4-methoxy-2-(2-nitro-vinyl)-benzene (18.7 g, 95 mmol) in THF (150 mL) by cannula and stir 2.5 h at ambient temperature. Cool the mixture to 0°C, cautiously add water (4.6 mL) followed by 2N aqueous NaOH (4.6 mL) and water (6.5 mL). Remove the precipitate by filtration and evaporate the filtrate to give the desired intermediate (16 g, 100 %). MS (ES+) *m/z*: 170 $(M+H)^+$.

***N*-(2,2-Dimethoxy-ethyl)-2,2,2-trifluoro-*N*-[2-(2-fluoro-5-methoxy-phenyl)-ethyl]-acetamide:** Dissolve 2-(2-fluoro-5-methoxyphenyl)-ethylamine (16 g, 95 mmol) and dimethoxy acetaldehyde (60 % aqueous, 21.5 mL, 142 mmol) in methanol (500 mL). After 1.5 h, cautiously add sodium borohydride (5.39 g, 142 mmol) at 0°C and then stir at ambient temperature for 3 h. Add acetone and evaporate the mixture. Dissolve the residue in DCM (250 mL), cool to 0°C and add triethylamine (26.5 mL, 190 mmol) and trifluoroacetic anhydride (20.1 mL, 142 mmol). After 30 min, wash the mixture with 1N aqueous HCl (4 x 100 mL), brine and saturated aqueous $NaHCO_3$. Dry the organic layer over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel to give the desired intermediate (19.7 g, 59%). MS (ES+) *m/z*: 322 $(M\text{-}OMe)^+$.

9-Fluoro-6-methoxy-3-(2,2,2-trifluoroacetyl)-2,3-dihydro-1*H*-benzo[*d*]azepine: Dissolve *N*-(2,2-dimethoxy-ethyl)-2,2,2-trifluoro-*N*-[2-(2-fluoro-5-methoxy-phenyl)-ethyl]-acetamide (5 g, 14.2 mmol) in chlorobenzene (100 mL). Add polyphosphoric acid (5 g) and P_2O_5 (2.5 g) and heat at 80°C for 2 h. Add water to the hot mixture, cool to

room temperature and extract with DCM. Dry the organic extracts over Na_2SO_4 and concentrate *in vacuo* to obtain the desired intermediate (3.0 g, 73%). MS (ES+) *m/z*: 290 $(M+H)^+$.

9-Fluoro-6-methoxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 9-fluoro-6-methoxy-3-(2,2,2-trifluoroacetyl)-2,3-dihydro-1*H*-benzo[*d*]azepine (9.4 g, 32.4 mmol) with 10 % Pd/C (dry basis, Degussa type, 1.4 g, 0.65 mmol) in EtOAc/ethanol (1:1, 200 mL) and stir at ambient temperature under a balloon of hydrogen for 4.5 h. Filter the mixture through a pad of silica gel and evaporate the filtrate to obtain the desired intermediate (8.6 g, 91%). MS (ES+) *m/z*: 292 $(M+H)^+$.

9-Fluoro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 9-fluoro-6-methoxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (8.1 g, 27.7 mmol) in DCM (250 mL), cool to 0°C and add boron tribromide (5.24 mL, 55.5 mmol). Stir at ambient temperature for 1.5 h, wash the mixture with brine, dry the organic layer over Na_2SO_4 and concentrate *in vacuo* to obtain the desired intermediate (7.6 g, 99%). MS (ES+) *m/z*: 278 $(M+H)^+$.

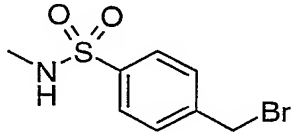
7-Chloro-9-fluoro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 9-fluoro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.0 g, 3.6 mmol) in toluene (36 mL) with diisopropylamine (41 µL, 0.29 mmol). Warm to 60°C and add dropwise a solution of sulfuryl chloride (0.32 mL, 3.97 mmol) in toluene (10 mL). After 2 h, wash the mixture with brine, dry the organic layer over Na_2SO_4 and evaporate onto silica gel. Purify by chromatography on silica gel eluting with EtOAc/hexane (0:1 to 1:0) to obtain the desired intermediate (1.0 g, 92%). MS (ES+) *m/z*: 312 $(M+H)^+$.

7-Chloro-9-fluoro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Cool a solution of 7-chloro-9-fluoro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2.5 g, 8.0 mmol), pyridine (3.25 mL, 40.2 mmol) and DCM (80 mL) at 0 °C and add dropwise

trifluoromethanesulfonic anhydride (2.43 mL, 14.5 mmol) over 20 min. Stir at room temperature for 1 h. Wash the reaction mixture sequentially with 1N aqueous HCl, saturated $NaHCO_3$ solution and brine. Dry the organic fraction over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (gradient from 19:1 to 1:1) to obtain the title compound (3.1 g, 87%).

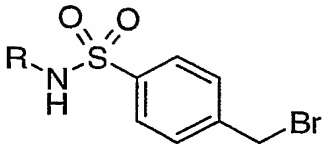
Preparation 7

4-Bromomethyl-*N*-methyl-benzenesulfonamide



Mix 4-(bromomethyl)benzenesulfonyl chloride (2.7 g, 10 mmol), anhydrous potassium carbonate (1.4 g, 10 mmol) and anhydrous THF (60 mL) under nitrogen. Cool the mixture in an ice bath, add dropwise a 2M solution of methylamine in THF, and stir at this temperature for 30 min. Remove the ice bath and stir at ambient temperature for 16 h. Dilute with EtOAc then wash with 1N aqueous HCl. Separate the organic layer, dry over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 4:1, 7:3 and 13:7) to obtain the title compound (1.5 g, 71%). MS (ES+) *m/z*: 266 $(M+H)^+$.

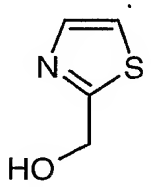
The compounds of Preparations 8-9 may be prepared essentially as described in Preparation 7 by using 4-(bromomethyl)benzenesulfonyl chloride and the appropriate amine. Yields and MS (ES+) data are shown in the Table below.



Prep.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
8	NH-CH_2CH_3	4-Bromomethyl-*N*-ethyl-benzenesulfonamide	43	278 $(M+H)^+$
9	NH-CH_2CH_2F	4-Bromomethyl-*N*-(2-fluoroethyl)-benzenesulfonamide	39	296 $(M+H)^+$

Preparation 10

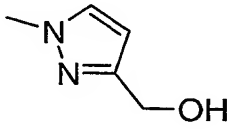
Thiazol-2-yl-methanol



Mix under nitrogen 2-thiazolecarboxaldehyde (1.1 g, 10 mmol) and ethanol (30 mL). Add sodium borohydride (416 mg, 11 mmol) at 0°C. Stir and warm the mixture slowly to ambient temperature for 12 h. Quench with saturated aqueous ammonium chloride and concentrate *in vacuo*. Dilute the residue with EtOAc and wash with brine. Dry the organic fraction over Na_2SO_4 and concentrate *in vacuo* to obtain the title compound as an oil (1.0 g, 87%). MS (ES+) *m/z*: 116 $(M+H)^+$.

Preparation 11

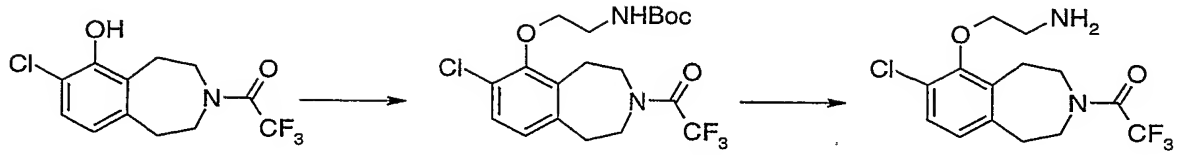
(1-Methyl-1*H*-pyrazol-3-yl)-methanol



Dissolve 3-dimethoxymethyl-1-methylpyrazole (1.562 g, 10 mmol) in acetone (100 mL), add *p*-toluenesulfonic acid (190 mg, 1.0 mmol) and stir at ambient temperature for 12 h. Remove volatiles *in vacuo*, dissolve the residue in EtOAc, wash with saturated aqueous $NaHCO_3$, dry over Na_2SO_4, filter and concentrate *in vacuo* to afford an oil. Dissolve the oil in methanol (15 mL), add sodium borohydride (567 mg, 15 mmol) and stir the reaction mixture at ambient temperature for 12 h. Remove volatiles *in vacuo*, dissolve the residue in EtOAc, wash with saturated aqueous $NaHCO_3$, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (6:1) to give the title compound as an oil (530 mg, 47%).

Preparation 12

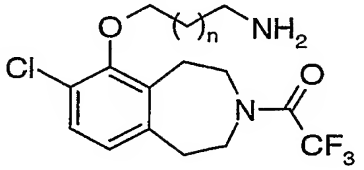
6-(2-Amino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



6-(2-*tert* Butoxycarbonylamino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to the General Procedure 4-3, using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (277 mg, 0.94 mmol) and *N*-(*tert*-butoxycarbonyl)ethanolamine (244 mg, 1.51 mmol) to give, after chromatography on silica gel eluting with hexane/EtOAc (1:0 and 3:1), the desired intermediate (392 mg, 95%). MS (ES+) *m/z*: 337 $(M+H\text{-}Boc)^+$.

6-(2-Amino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 6-(2-*tert*-butoxycarbonylamino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (997 mg, 2.28 mmol) in 4M hydrogen chloride in dioxane (15 mL) and stir at ambient temperature for 30 min. Concentrate to obtain the hydrochloride salt. Dissolve the salt in DCM and wash with saturated aqueous $NaHCO_3$. Extract the basic aqueous layer with DCM. Dry the combined organic extracts over $MgSO_4$, and concentrate *in vacuo* to afford the title compound (731 mg, 95%). MS (ES+) *m/z*: 337 $(M+H)^+$.

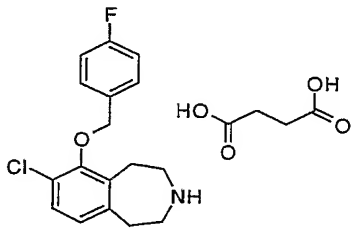
The compounds of Preparations 13-14 may be prepared essentially as described in Preparation 12 by using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate alcohol. Overall yields and MS (ES+) data are shown in the Table below.



Prep.	n	Compound	Yield (%)	MS (ES+) *m/z*
13	1	6-(3-Amino-propoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine	94	351 $(M+H)^+$
14	2	6-(4-Amino-butoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine	89	365 $(M+H)^+$

Example 7

7-Chloro-6-(4-fluorobenzyloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



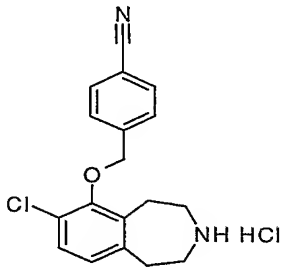
Prepare a slurry of sodium hydride (60% in mineral oil; 99 mg, 2.5 mmol) in DMF (4 mL) and heat to 65° C. Add a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-hydroxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (250 mg, 0.84 mmol) in DMF (5 mL) dropwise and stir for 1 h. Add a solution of 4-fluorobenzyl bromide (191 mg, 1.0 mmol) in DMF (1 mL), stir at 65°C for 1.5 h and cool to ambient temperature. Add water (1 mL) and concentrate the mixture to an oily residue. Partition the residue between EtOAc/hexane (1:1) and water. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Dissolve the residue in DCM, wash with 2N aqueous NaOH, dry the organic layer over Na_2SO_4, filter, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (20:1, 10:1 and 7:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(4-fluorobenzyloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil.

Use a method similar to General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(4-fluorobenzyloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by SCX chromatography followed by chromatography on silica gel eluting with DCM/2M ammonia in methanol (1:0, 50:1, 20:1, 15:1 and 10:1) to give the free base of

the title compound. Use a method similar to the General Procedure 2-1 to give the title compound as a white solid (178 mg, 50%). MS (ES+) *m/z*: 306 $(M+H)^+$.

Example 8

7-Chloro-6-(4-cyanobenzyloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

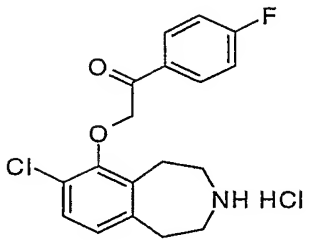


Combine 3-*tert*-butoxycarbonyl-7-chloro-6-hydroxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.67 mmol), potassium carbonate (111 mg, 0.8 mmol), and 4-cyanobenzyl bromide (263 mg, 1.34 mmol) in DMSO (5 mL) and heat the stirred mixture to 100° C for 24 h. Cool to ambient temperature and partition the mixture between water and EtOAc/hexane (1:1). Wash the organic layer with brine and dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (5:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(4-cyanobenzyloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil.

Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(4-cyanobenzyloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by SCX chromatography to give the free base of the title compound. Use a method similar to the General Procedure 2-2 to give the title compound as an off-white solid (66 mg, 27%). MS (ES+) *m/z*: 313 $(M+H)^+$.

Example 9

7-Chloro-6-[2-(4-fluorophenyl)-2-oxo-ethoxy)]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

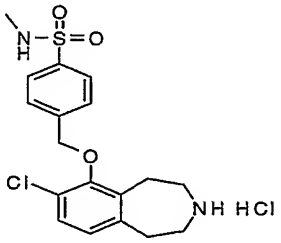


Use a method similar to the General Procedure 4-1, using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (294 mg, 1.0 mmol) and 2-bromo-4'-fluoroacetophenone (260 mg, 1.2 mmol) to give, after purification by chromatography on silica gel eluting with hexane/EtOAc (7:1), 7-chloro-6-[2-(4-fluorophenyl)-2-oxo-ethoxy)]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a solid (402 mg, 93%). MS (ES+) *m/z*: 430 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[2-(4-fluorophenyl)-2-oxo-ethoxy)]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (402 mg, 0.93 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (96:4) to give the free base of the title compound (278 mg, 89%). MS (ES+) *m/z*: 334 $(M+H)^+$. Use a method similar to the General Procedure 2-3 to give the title compound.

Example 10

7-Chloro-6-(4-methylsulfamoyl-benzyloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

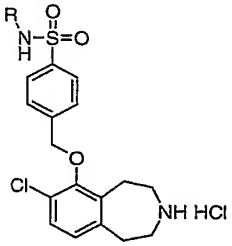


Dissolve under nitrogen 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.68 mmol) in acetone (30 mL). Add powdered anhydrous potassium carbonate (276 mg, 2.0 mmol) and powdered potassium iodide (11.3 mg, 0.068 mmol) followed by 4-bromomethyl-*N*-methyl-benzenesulfonamide (528 mg,

2.0 mmol). Stir the reaction mixture at ambient temperature for 12 h. Concentrate *in vacuo*, dilute with EtOAc and wash twice with 1N aqueous HCl. Separate the organic layer, dry over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 4:1) to obtain 7-chloro-6-(4-methylsulfamoyl-benzyloxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (201 mg, 60%).

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-(4-methylsulfamoyl-benzyloxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (196 mg, 0.41 mmol). Purify by SCX column to give the free base of the title compound (110 mg, 70%). MS (ES+) *m/z*: 381 $(M+H)^+$. Use a method similar to the General Procedure 2-2 to obtain the title compound.

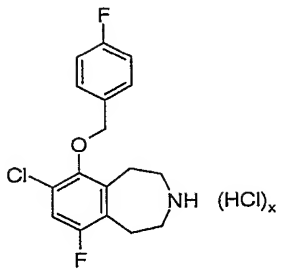
Examples 11-12 may be prepared essentially as described in Example 10 by using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate bromide. MS (ES+) data are shown in the Table below.



Ex.	NH-R	Compound	MS (ES+) *m/z*
11	NH-CH_2-CH_3	7-Chloro-6-(4-ethylsulfamoyl-benzyloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	395 $(M+H)^+$
12	NH-CH_2-CH_2F	7-Chloro-6-[4-(2-fluoroethylsulfamoyl)-benzyloxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	413 $(M+H)^+$

Example 13 Allen 1

7-Chloro-9-fluoro-6-(4-fluorobenzyloxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

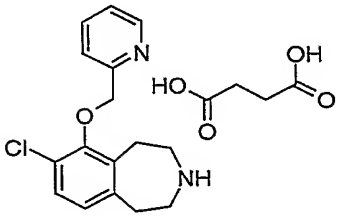


Dissolve 7-chloro-9-fluoro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.25 g, 0.8 mmol) in DMF (8 mL), add potassium carbonate (0.56 g, 4.0 mmol) and 4-fluorobenzyl bromide (0.46 mL, 2.4 mmol). After 14 h at 90 °C, dilute with ether and wash with brine. Dry the organic layer over Na_2SO_4 and evaporate onto silica gel. Purify by chromatography on silica gel eluting with EtOAc/hexane (0:1 to 1:0) to obtain 7-chloro-9-fluoro-6-(4-fluorobenzyloxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine.

Use a method similar to the General Procedure 1-1, using 7-chloro-9-fluoro-6-(4-fluorobenzyloxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, to give the free base of the title compound. Use a method similar to the General Procedure 2-2 to obtain the title compound (275 mg, 95%). HRMS calc'd for $C_{17}H_{17}NOF_2Cl$ 324.0902, found 324.0957.

Example 14

7-Chloro-6-(pyridin-2-ylmethoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



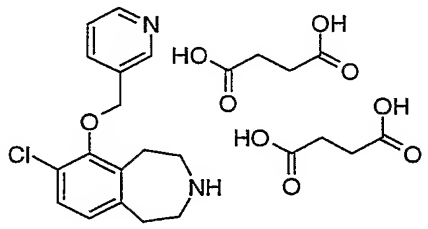
Prepare a slurry of sodium hydride (60% in mineral oil, 168 mg, 4.2 mmol) in DMF (4 mL) and heat to 65° C. Add dropwise a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-hydroxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (250 mg, 0.84 mmol) in DMF (5 mL) and stir for 1 h. Add a solution of 2-(bromomethyl)-pyridine hydrobromide (256

mg, 1 mmol) in DMF (1 mL), stir at 65° C for 0.5 h and cool to ambient temperature. Add water (1 mL) and concentrate the reaction mixture to an oily residue. Partition the residue between EtOAc/hexane (1:1) and water. Dry the organic layer over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1, 5:1 and 3:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(pyridin-2-ylmethoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil.

Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(pyridin-2-ylmethoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by SCX chromatography to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound as a white solid (228 mg, 67%). MS (ES+) *m/z*: 289 $(M+H)^+$.

Example 15

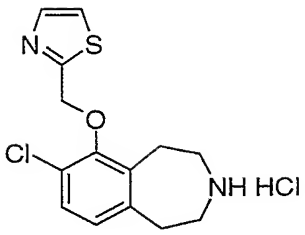
7-Chloro-6-(pyridin-3-ylmethoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Disuccinate



Use a method similar to the Example 14, using 3-*tert*-butoxycarbonyl-7-chloro-6-hydroxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (250 mg, 0.84 mmol) and 3-(bromomethyl)-pyridine hydrobromide (256 mg, 1 mmol) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 with two equivalents of succinic acid to give the title compound as a white solid (354 mg, 80%). MS (ES+) *m/z*: 289 $(M+H)^+$.

Example 16

7-Chloro-6-(thiazol-2-ylmethoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

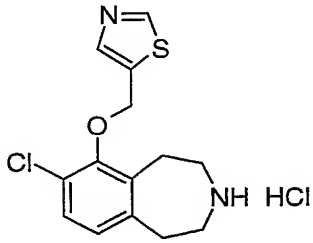


Use a method similar to the General Procedure 4-2, using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and thiazol-2-yl-methanol (86.2 mg, 0.75 mmol) to give, after chromatography on silica gel eluting with hexane/EtOAc (9:1 and 7:3), 7-chloro-6-(thiazol-2-ylmethoxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (163 mg, 61%). MS (ES+) *m/z* 391 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-(thiazol-2-ylmethoxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (94:6) to obtain the free base of the title compound (99 mg, 81%). MS (ES+) *m/z*: 295 $(M+H)^+$. Use a method similar to the General Procedure 2-2 to give the title compound.

Example 17

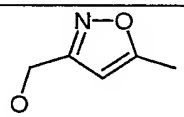
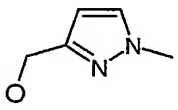
7-Chloro-6-(thiazol-5-ylmethoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the General Procedure 4-2, using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (294 mg, 1.0 mmol) and 5-hydroxymethylthiazole (127 mg, 1.1 mmol) to give, after chromatography on silica gel eluting with EtOAc/hexane (1:3), 7-chloro-6-(thiazol-5-ylmethoxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (350 mg, 89%). MS (ES+) *m/z*: 391 $(M+H)^+$.

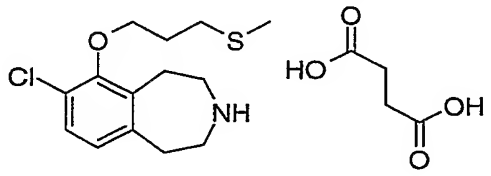
Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-(thiazol-5-ylmethoxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (350 mg, 0.90 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to give the free base of the title compound (203 mg, 76%). MS (ES+) *m/z*: 295 $(M+H)^+$. Use a method similar to the General Procedure 2-2 to give the title compound.

Examples 18-19 may be prepared essentially as described in Example 17 by using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate alcohol. Overall yields and MS (ES+) data are shown in the Table below.

Ex.	O-R	Compound	Yield (%)	MS (ES+) *m/z*
18		7-Chloro-6-(5-methyl-isoxazol-3-ylmethoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	47	293 $(M+H)^+$
19		7-Chloro-6-(1-methyl-1*H*-pyrazol-3-ylmethoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	39	292 $(M+H)^+$

Example 20

7-Chloro-6-(3-methylthio-propoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

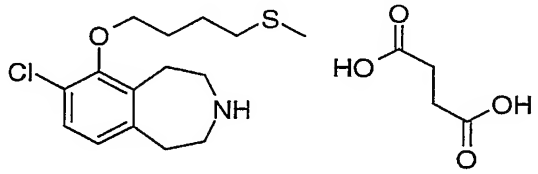


Use a method similar to the General Procedure 4-2, using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-(methylthio)-1-propanol (191 mg, 1.8 mmol) to give, after chromatography on silica gel eluting with EtOAc/hexane (1:8), 7-chloro-6-(3-methylthio-propoxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (65 mg, 14%).

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-(3-methylthio-propoxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (65 mg, 0.17 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (94:6) to give the free base of the title compound (25 mg, 51%). MS (ES+) *m/z*: 286 $(M+1)^+$. Use a method similar to the General Procedure 2-1 to give the title compound.

Example 21

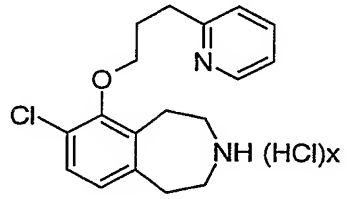
7-Chloro-6-(4-methylthio-butoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the Example 20, using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-(methylthio)-1-butanol to give the title compound. MS (ES+) *m/z*: 300 $(M+1)^+$.

Example 22

7-Chloro-6-(3-pyridin-2-yl-propoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

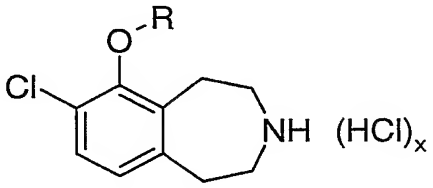


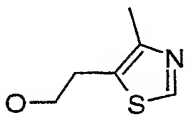
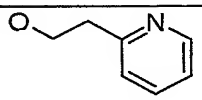
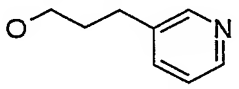
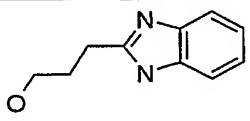
Use a method similar to the General Procedure 4-3, using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (50 mg, 0.17 mmol) and 3-(2-pyridyl)-1-propanol (35 mg, 0.255 mmol) to give, after reverse phase HPLC (10-95% of solvent B in 12.8 min, 25 mL/min; solvent A: water, 0.1% trifluoroacetic acid; solvent B: acetonitrile, 0.1% trifluoroacetic acid; column: YMC SH-341-5, S-5□m, 12 nm, 100 x

20 mm), 7-chloro-6-(3-pyridin-2-yl-propoxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine.

Use a method similar to the General Procedure 1-1, using 7-chloro-6-(3-pyridin-2-yl-propoxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the free base of the title compound. Use a method similar to the General Procedure 2-2 to give the title compound as a solid (26 mg, 39%). MS (ES+) *m/z*: 317 $(M+H)^+$.

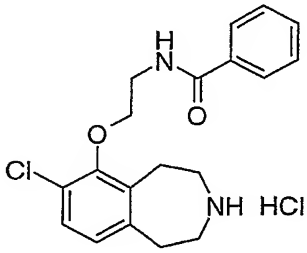
Examples 23-26 may be prepared essentially as described in Example 22 by using 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate alcohol. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	O-R	Compound	Yield (%)	MS (ES+) *m/z*
23		7-Chloro-6-[2-(4-methyl-thiazol-5-yl)-ethoxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	83	323 $(M+H)^+$
24		7-Chloro-6-(2-pyridin-2-yl-ethoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	83	303 $(M+H)^+$
25		7-Chloro-6-(3-pyridin-3-yl-propoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	83	317 $(M+H)^+$
26		6-[3-(1*H*-Benzimidazol-2-yl)-propoxy]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	8	356 $(M+H)^+$

Example 27

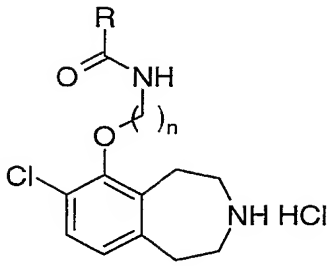
6-(2-Benzoylamino-ethoxy)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

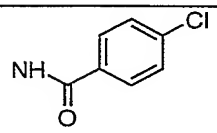
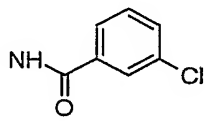
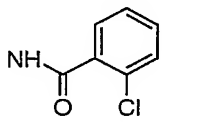
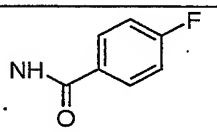
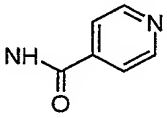
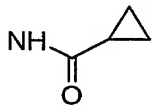
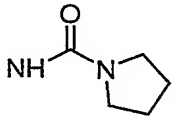
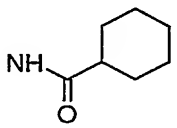


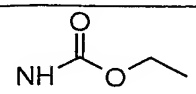
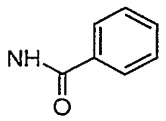
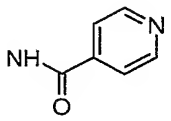
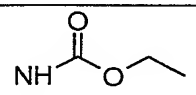
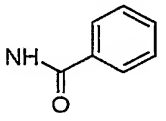
Combine benzoyl chloride (19.3 mg, 0.137 mmol), PS-morpholine (109 mg, 0.272 mmol), 6-(2-amino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (46 mg, 0.137 mmol) in DCM (1.5 mL) and stir at ambient temperature for 16 h. Filter the resin, wash with DCM and concentrate *in vacuo*. Purify by reverse phase HPLC (10-95% of solvent B in 12.8 min, 25 mL/min; solvent A: water, 0.1% trifluoroacetic acid; solvent B: acetonitrile, 0.1% trifluoroacetic acid; column: YMC SH-341-5, S-5μm, 12 nm, 100 x 20 mm) to give 6-(2-benzoylamino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine.

Use a method similar to the General Procedure 1-1, using 6-(2-benzoylamino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the free base of the title compound. Use a method similar to the General Procedure 2-2 to give the title compound as a solid (51 mg, 98%). MS (ES+) *m/z*: 345 $(M+H)^+$.

Examples 28-40 may be prepared essentially as described in Example 27, using 6-(2-amino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine or 6-(3-amino-propoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine or 6-(4-amino-butoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate acyl chloride. Overall yields and MS (ES+) data are shown in the Table below.

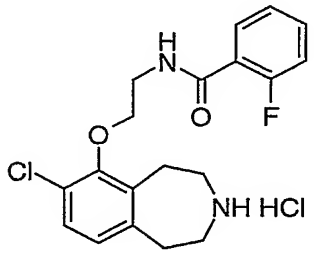


Ex.	NH-CO-R	n	Compound	Yield (%)	MS (ES+) *m/z*
28		2	7-Chloro-6-[2-(4-chlorobenzoylamino)-ethoxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	46	380 $(M+H)^+$
29		2	7-Chloro-6-[2-(3-chlorobenzoylamino)-ethoxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	63	380 $(M+H)^+$
30		2	7-Chloro-6-[2-(2-chlorobenzoylamino)-ethoxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	18	380 $(M+H)^+$
31		2	7-Chloro-6-[2-(4-fluorobenzoylamino)-ethoxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	18	363 $(M+H)^+$
32		2	7-Chloro-6-{2-[(pyridine-4-carbonyl)-amino]-ethoxy}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	4	346 $(M+H)^+$
33		2	7-Chloro-6-[2-(cyclopropanecarbonyl-amino)-ethoxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	47	309 $(M+H)^+$
34		2	7-Chloro-6-{2-[(pyrrolidine-1-carbonyl)-amino]-ethoxy}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	6	338 $(M+H)^+$
35		2	7-Chloro-6-[2-(cyclohexanecarbonyl-amino)-ethoxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	40	351 $(M+H)^+$

Ex.	NH-CO-R	n	Compound	Yield (%)	MS (ES+) *m/z*
36		3	7-Chloro-6-(3-ethoxycarbonylamino-propoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	63	327 $(M+H)^+$
37		3	6-(3-Benzoylamino-propoxy)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	72	359 $(M+H)^+$
38		3	7-Chloro-6-{3-[(pyridine-4-carbonyl)-amino]-propoxy}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	12	360 $(M+H)^+$
39		4	7-Chloro-6-(4-ethoxycarbonylamino-butoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	49	341 $(M+H)^+$
40		4	6-(4-Benzoylamino-butoxy)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	56	373 $(M+H)^+$

Example 41

7-Chloro-6-[2-(2-fluorobenzoylamino)-ethoxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



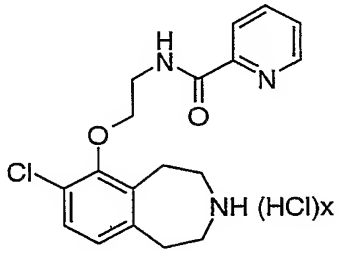
Dissolve 6-(2-amino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.297 mmol) in DCM (5 mL). Add 2-fluorobenzoyl chloride (39 μL, 0.326 mmol), triethylamine (62 μL, 0.445 mmol) and stir at ambient temperature for 72 h under nitrogen atmosphere. Dilute with DCM, add 1M aqueous HCl and extract the aqueous phase with DCM. Dry the combined organic extracts over $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with

hexane/EtOAc (7:3 and 2:1) to give 7-chloro-6-[2-(2-fluorobenzoylamino)-ethoxy]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111 mg, 82%).

Use a method similar to the General Procedure 1-1, using 7-chloro-6-[2-(2-fluorobenzoylamino)-ethoxy]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the free base of the title compound. Use a method similar to the General Procedure 2-2 to give the title compound as a solid (112 mg, 95%). MS (ES+) *m/z*: 363 $(M+H)^+$.

Example 42

7-Chloro-6-{2-[(pyridine-2-carbonyl)-amino]-ethoxy}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



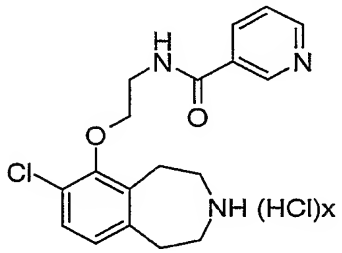
Combine picolinic acid (40 mg, 0.327 mmol), EDC (57 mg, 0.297 mmol) and HOBT (40 mg, 0.297 mmol) in DCM (3 mL). Stir for 10 min at ambient temperature. Add 6-(2-amino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.297 mmol). Stir for 16 h at ambient temperature. Dilute with DCM, add water and extract the aqueous layer with DCM. Wash the combined organic extracts with 1M aqueous NaOH and brine. Dry the organic layer over $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (3:2) to give 7-chloro-6-{2-[(pyridine-2-carbonyl)-amino]-ethoxy}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (94 mg, 74%).

Use a method similar to the General Procedure 1-1, using 7-chloro-6-{2-[(pyridine-2-carbonyl)-amino]-ethoxy}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the free base of the title compound. Use a method similar to the

General Procedure 2-2 to give the title compound as a solid (81 mg, 72%). MS (ES+) *m/z*: 346 $(M+H)^+$.

Example 43

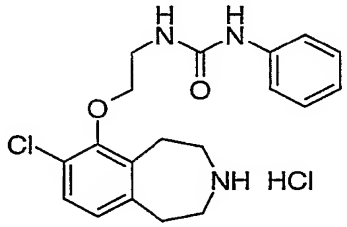
7-Chloro-6-{2-[(pyridine-3-carbonyl)-amino]-ethoxy}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to Example 42, using nicotinic acid (40 mg, 0.327 mmol) and 6-(2-amino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.297 mmol) to give the title compound as a solid (105 mg, 93%). MS (ES+) m/z: 346 $(M+H)^+$.

Example 44

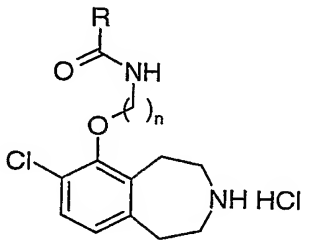
7-Chloro-6-[2-(3-phenyl-ureido)-ethoxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

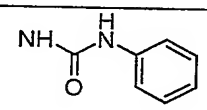
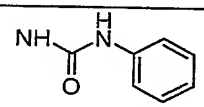


Combine phenyl isocyanate (16.3 mg, 0.137 mmol), 6-(2-amino-ethoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (46 mg, 0.137 mmol) in DCM (1.5 mL) and stir at ambient temperature for 16 h. Concentrate *in vacuo*. Purify by reverse phase HPLC (10-95% of solvent B in 12.8 min, 25 mL/min; solvent A: water, 0.1% trifluoroacetic acid; solvent B: acetonitrile, 0.1% trifluoroacetic acid; column: YMC SH-341-5, S-5μm, 12 nm, 100 x 20 mm) to give 7-chloro-6-[2-(3-phenyl-ureido)-ethoxy]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine.

Use a method similar to the General Procedure 1-1, using 7-chloro-6-[2-(3-phenyl-ureido)-ethoxy]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the free base of the title compound. Use a method similar to the General Procedure 2-2 to give the title compound as a solid (8 mg, 15%). MS (ES+) *m/z*: 360 $(M+H)^+$.

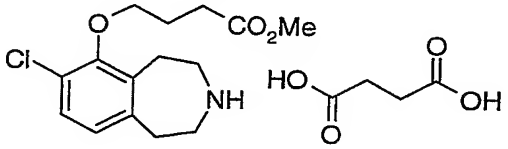
Examples 45-46 may be prepared essentially as described in Example 44 by using phenyl isocyanate and the appropriate 6-(3-amino-propoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine or 6-(4-amino-butoxy)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	NH-CO-R	n	Compound	Yield (%)	MS (ES+) *m/z*
45		3	7-Chloro-6-[3-(3-phenyl-ureido)-propoxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	36	374 $(M+H)^+$
46		4	7-Chloro-6-[4-(3-phenyl-ureido)-butoxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	28	388 $(M+H)^+$

Example 48

7-Chloro-6-(3-methoxycarbonyl-propyloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Add methyl 4-bromobutyrate (1.9 mL, 10.4 mmol) to a mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-hydroxy-2,3,4,5-tetrahydro-benzo[*d*]azepine (310 mg, 1.0 mmol), DBU (0.23 mL, 1.6 mmol) and DMF (10 mL) at ambient temperature under nitrogen. Stir the reaction mixture for 16 h. Dilute with hexane/EtOAc (1:1, 60 mL), wash the mixture with 10% aqueous NaCl (4 x 25 mL), dry the organic layer over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 2:3) to obtain 3-*tert*-butoxycarbonyl-7-chloro-6-(3-methoxycarbonyl-propyloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (303 mg, 73%). MS (ES+) *m/z*: 398 $(M+H)^+$.

Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(3-methoxycarbonyl-propyloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (295 mg, 0.74 mmol). Purify by SCX chromatography followed by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99:1 to 90:10) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound (160 mg, 52%). MS (ES+) *m/z*: 298 $(M+H)^+$.

General Procedure 5-1

Dissolve the appropriately substituted 3-(2,2,2-trifluoroacetyl)-6-trifluoromethane-sulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1 equiv.), palladium(II) acetate (0.1-0.4 equiv.), BINAP (0.2-0.8 equiv.; BINAP/catalyst ratio 2:1) and cesium carbonate (1.4-3.0 equiv.) in toluene (0.2-0.05 M solution). Add the amine (1-3 equiv.), degas the mixture with vacuum/nitrogen or argon purge and heat at 80-110°C for 4-16 h. Cool the mixture to ambient temperature, dilute with EtOAc, filter through a pad of silica gel or through Celite® washing with EtOAc or ether, and evaporate the solvent to obtain the crude mixture. Alternatively, partition the reaction mixture between brine or saturated aqueous $NaHCO_3$ and EtOAc, ether or DCM, dry the organic layer over Na_2SO_4, and concentrate to obtain the crude mixture. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc mixtures and further SCX chromatography if needed.

General Procedure 5-2

Dissolve the appropriately substituted 3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1 equiv.), tris(dibenzylideneacetone)dipalladium(0) (0.1-0.5 equiv.), BINAP (0.2-1.0 equiv.; BINAP/catalyst ratio 2:1) and cesium carbonate (1.4 equiv.) in toluene (0.05-0.5 M solution). Degas under vacuum and fill three times with nitrogen. Add the appropriately substituted amine (1.0-5.0 equiv.) and heat the mixture to 80-100°C for 2-16 h in a sealed flask under a nitrogen atmosphere. Cool the reaction flask to ambient temperature, dilute the mixture with EtOAc or DCM, filter through Celite® and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc mixtures and further SCX chromatography if needed.

General Procedure 5-3

Add the appropriately substituted 3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1 equiv.), the appropriate amine (1.2-3.0 equiv.), palladium(II) acetate (0.2-0.4 equiv.), tris(dibenzylideneacetone)dipalladium(0) (0.1-0.2 equiv.), BINAP (0.6-1.2 equiv.; BINAP/catalysts ratio 2:1), cesium carbonate (2-2.5 equiv.) and toluene or 1,4-dioxane (0.05-0.2 M solution) to a flask, degas and fill three times with nitrogen. Heat the mixture at 80-100°C for 10-16 h. Dilute the mixture with EtOAc, wash with saturated aqueous $NaHCO_3$ and brine, dry over Na_2SO_4, filter and concentrate *in vacuo* to give the crude mixture. Alternatively remove the volatiles from the reaction mixture to give directly the crude mixture, or filter the reaction mixture through Celite® and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc mixtures and further SCX chromatography if needed.

General Procedure 5-4

Combine 6-amino-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*] azepine, the appropriate bromide (1.0-2.0 equiv.), potassium or cesium carbonate (1.0-2.0 equiv.) and toluene, DMF or acetonitrile in a sealed tube and heat at

50-150°C for 3-72 h. Cool to ambient temperature and evaporate the solvent *in vacuo* to obtain the crude mixture. Alternatively, partition the reaction mixture between diethyl ether/brine (1:1), dry the organic layer over anhydrous Na_2SO_4 and concentrate to obtain the crude mixture. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1, 4:1, 7:3 and 3:2).

General Procedure 6-1

Dissolve 4-(*tert*-butoxycarbonylamino-methyl)-benzoic acid (1 equiv.), HATU (1 equiv.), DIEA (2 equiv.) and the appropriately substituted amine (1 equiv.) in DCM or DCM/DMF and stir at ambient temperature for 4-16 h. Concentrate *in vacuo*, dissolve the residue in DCM and wash successively with saturated aqueous $NaHCO_3$, 1N aqueous HCl, water, brine, and dry over Na_2SO_4. Filter and concentrate the solution and use the material without further purification. Deprotect the residue using the General Procedure 1-5 and purify by SCX chromatography.

General Procedure 6-2

Dissolve 4-(*tert*-butoxycarbonylamino-methyl)-benzoic acid or 5-(*tert*-butoxycarbonylamino-methyl)-pyridine-2-carboxylic acid lithium salt (1 equiv.), HATU (1 equiv.), DIEA (2 equiv.) and the appropriately substituted amine (1 equiv.) in DCM or DCM/DMF and stir at ambient temperature for 4-16 h. Concentrate *in vacuo*, dissolve the residue in DCM and wash successively with saturated aqueous $NaHCO_3$, water, brine, and dry over Na_2SO_4. Filter and concentrate the solution and use the material without further purification. Deprotect the residue using the General Procedure 1-5 and purify by SCX chromatography.

General Procedure 6-3

Dissolve the appropriately substituted acetophenone (1.0-1.2 equiv.) in THF, add titanium(IV) ethoxide (33-35% TiO_2, 2.0 equiv.) and the corresponding (*R*)-2-methyl-2-propanesulfinamide or (*S*)-2-methyl-2-propanesulfinamide (1.0 equiv.). Heat the mixture to 40-60 °C for 2–16 h under a nitrogen atmosphere. Cool the reaction to –78°C, then add the cold mixture over 3-10 min to a slurry of THF/$NaBH_4$ (2-4 M) at –78 °C. Allow the

mixture to warm up to ambient temperature over 2-16 h. Pour the mixture into brine, filter the resulting slurry through Celite® and wash thoroughly with EtOAc. Concentrate *in vacuo*. Dilute the oil with EtOAc, wash with brine and extract the aqueous phase with EtOAc. Dry the combined organic extracts over Na_2SO_4 and concentrate *in vacuo*. Purify the crude sulfinamide on silica gel eluting with hexane/EtOAc mixtures to obtain the major diastereomer. Dissolve the major diastereomer in excess of 4M hydrogen chloride in dioxane, stir the mixture for 1 h and concentrate *in vacuo* to a solid. Slurry the solid in diethyl ether, then filter *in vacuo* to obtain the hydrochloride salt of the desired amine. The free base of the amine is prepared either via SCX chromatography or by basic extraction.

General Procedure 6-4

Add the appropriately substituted benzonitrile portion wise to a flask containing a slurry of lithium aluminum hydride (3.0–6.0 equiv.) in diethyl ether (0.1–0.3 M solution) under a nitrogen atmosphere. Stir the mixture for 1 h and quench slowly with water (0.5-2.0 mL), followed by 5N aqueous NaOH (0.5-2.0 mL). Filter the slurry through Celite® and wash the cake with diethyl ether. Concentrate *in vacuo* to obtain the desired amine. If additional purification is needed, dissolve the amine in ether and add an excess of 2M hydrogen chloride in ether. Filter to obtain the desired amine as the hydrochloride salt. Prepare the free base by using SCX chromatography or by dissolving the hydrochloride salt in an aqueous solution of cesium carbonate (1.0–5.0 equiv.) or saturated aqueous $NaHCO_3$ (1.0–5.0 equiv.). Extract the mixture with DCM or toluene, dry over Na_2SO_4 and concentrate *in vacuo* to obtain the amine.

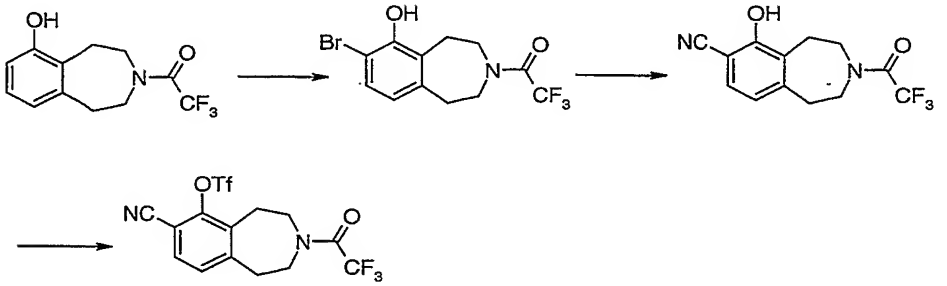
General Procedure 6-5

Add BH_3-THF complex (1-3 equiv., 1M solution in THF) dropwise to a solution of appropriately substituted benzonitrile in anhydrous THF at room temperature then stir overnight. Alternatively the reaction can be heated at reflux overnight. Add either methanol or aqueous HCl (3 equiv.) cautiously at room temperature and stir vigorously until gaseous evolution stops. Concentrate *in vacuo*, basify and then extract into EtOAc. Wash the organic phase with brine, dry over $MgSO_4$ and concentrate *in vacuo*. Purify by

SCX chromatography eluting with methanol followed by a solution of ammonia in methanol (3-7 M) to give the desired benzylamine.

Preparation 15

7-Cyano-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



7-Bromo-6-hydroxy-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine:

Dissolve 6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (18 g, 69.4 mmol) and DIEA (0.98 mL) in DCM (1.4 L). Add dropwise a solution of NBS (12.4 g, 69.4 mmol) in DCM (500 mL) over 75 min. Stir the reaction mixture at ambient temperature for 1 h, pour into water (500 mL) and extract the mixture with DCM. Wash the organic fraction with brine, dry over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to give the desired intermediate as a white solid (20.9 g, 89%). MS (ES-) *m/z*: 337 $(M-H)^-$.

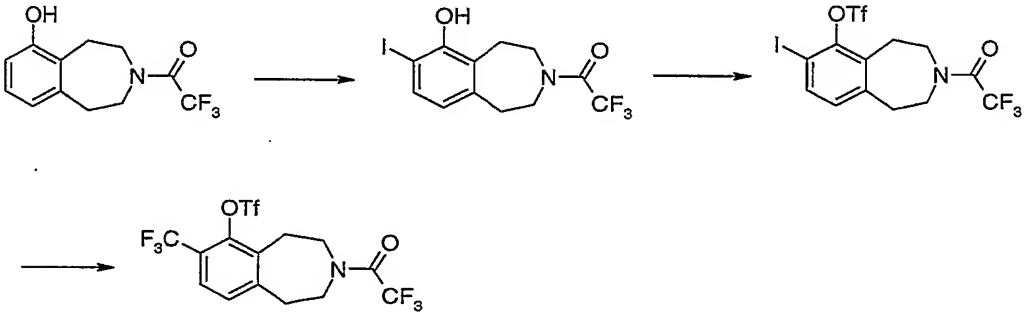
7-Cyano-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine:

Add copper nitrile (2.6 g, 28 mmol) to a solution of 7-bromo-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2.4 g, 7.0 mmol) in anhydrous NMP (45 mL), degas and purge with nitrogen and heat to 150°C for 18 h. Allow the reaction mixture to cool to ambient temperature and then dilute with EtOAc/heptane (2:1) and filter through a silica pad. Dilute the filtrate with water, and extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over $MgSO_4$, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/heptane (1:4 to 1:1) to obtain the desired intermediate as an orange oil (1.7 g, 86%). MS (ES-) *m/z*: 283 $(M-H)^-$.

7-Cyano-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add dry pyridine (3 mL) to 7-cyano-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.1 g, 3.9 mmol) in anhydrous DCM (45 mL) and cool to 0 °C. Add slowly trifluoromethanesulfonic anhydride (1.3 mL, 7.7 mmol), allow the reaction mixture to warm to ambient temperature and stir for 3 h. Dilute with DCM and wash with 2N aqueous HCl. Dry the organic layer over $MgSO_4$, filter and concentrate *in vacuo* to obtain the title compound as an orange/brown oil (1.6 g, 100%) that was used without purification. MS (ES-) *m/z*: 415 $(M-H)^-$.

Preparation 16

3-(2,2,2-Trifluoroacetyl)-6-trifluoromethanesulfonyloxy-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



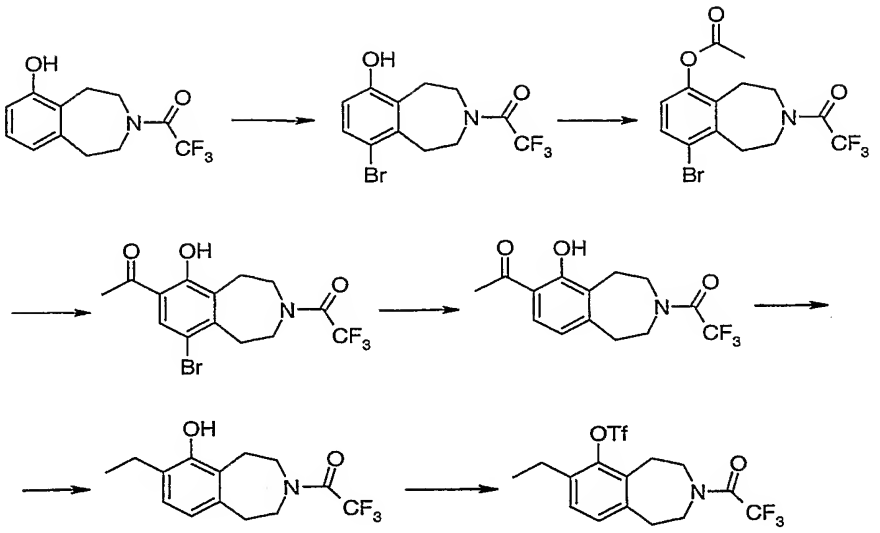
6-Hydroxy-7-iodo-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add 6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.037 g, 4.0 mmol) and diisopropylamine (60.7 mg, 0.6 mmol) to anhydrous DCM (350 mL) and stir at 10-20 °C. Add slowly a solution of *N*-iodosuccinimide (1.035 g, 4.6 mmol) in DCM (100 mL) over a period of 3 h. Stir the reaction mixture overnight and gradually warm to ambient temperature. Quench the reaction with saturated aqueous $NaHCO_3$, separate the organic layer, wash the organic layer with 0.1N aqueous HCl, brine, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:20 to 1:10) to give the desired intermediate as a white solid (1.0 g, 65%). MS (ES+) *m/z*: 386 $(M+H)^+$.

7-Iodo-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add triethylamine (496 mg, 4.90 mmol) to a solution of 6-hydroxy-7-iodo-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (945 mg, 2.45 mmol) in DCM (30 mL) at 0 °C. Add dropwise trifluoromethanesulfonic anhydride (1.244 g, 4.41 mmol) and stir at 0°C for 1 h. Warm to ambient temperature overnight. Dilute the mixture with DCM, wash with water, saturated aqueous $NaHCO_3$ and brine. Dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:6) to give the desired intermediate as a white solid (1.246 g, 98%). MS (ES+) *m/z*: 518 $(M+H)^+$.

3-(2,2,2-Trifluoroacetyl)-6-trifluoromethanesulfonyloxy-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add CuI (367 mg, 1.93 mmol), methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (1.852 g, 9.64 mmol) and HMPA (1.728 g, 9.64 mmol) to a solution of 7-iodo-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.246 g, 2.41 mmol) in DMF (8 mL) and heat the mixture at 70 °C for 1.5 h. Add same amount of CuI, methyl 2,2-difluoro-2-(fluorosulfonyl)acetate, and HMPA and stir further for 4 h. Cool the mixture to ambient temperature, quench with saturated aqueous ammonium chloride, separate the organic layer, and extract the aqueous layer with EtOAc three times. Combine the organic layers, wash with saturated aqueous $NaHCO_3$, brine, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:20 to 1:10) to give the title compound as a white solid (321 mg, 29%) and to recover the starting material (741 mg, 59%). MS (ES+) *m/z*: 460 $(M+H)^+$.

Preparation 17

7-Ethyl-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



9-Bromo-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add dropwise bromine (10.8 mL, 0.21 mol) in acetonitrile (260 mL) to a slurry of 6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (51.8 g, 0.2 mol) in acetonitrile (400 mL) at 0 °C cooling with ice-water to keep the temperature between 2-5°C. Warm the reaction to ambient temperature and stir for 30 min. Pour the mixture into ice-cold water (2 L) to obtain a white precipitate. Collect the solid by vacuum filtration, wash with water and dry under vacuum at 105 °C. Recrystallize the crude material in toluene/heptane and cool the mixture in an ice bath. Collect the solid by vacuum filtration, wash with heptane and dry under vacuum at 105 °C to obtain the desired intermediate as a white solid (54.63 g, 81%). MS (ES+) *m/z*: 338 $(M+H)^+$.

6-Acetoxy-9-bromo-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Under nitrogen atmosphere, mix 9-bromo-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (6 g, 17.8 mmol), anhydrous pyridine (0.06 mL, 0.72 mmol), DMAP (222 mg, 1.8 mmol) and acetic anhydride (30 mL). Heat the mixture at reflux for 8 h and then stir at ambient temperature for another 8 h. Concentrate *in vacuo*, dilute the residue in EtOAc, wash with 1N aqueous HCl, and then with saturated aqueous $NaHCO_3$. Dry the organic layer over Na_2SO_4, filter, and concentrate *in vacuo* to obtain the desired intermediate (5.64 g, 84%) that was used without further purification. MS (ES+) *m/z*: 380 $(M+H)^+$.

7-Acetyl-9-bromo-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Under nitrogen atmosphere, mix 6-acetoxy-9-bromo-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2.8 g, 7.4 mmol) and nitrobenzene (5 mL). Add anhydrous aluminum chloride (980 mg, 7.4 mmol). Heat at ~180°C for 2 h. Cool the mixture to ambient temperature. Add concentrated HCl (10 mL) dropwise. Stir the mixture for 30 min. Add 1N aqueous HCl then extract with EtOAc. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (0:1 to 1:4) to afford the desired intermediate (833 mg, 30%). MS (ES-) *m/z*: 378 $(M-H)^-$.

7-Acetyl-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Mix 7-acetyl-9-bromo-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (833 mg, 2.2 mmol), tetrakis(triphenylphosphine)palladium(0) (150 mg, 0.13 mmol) and sodium formate (224 mg, 3.3 mmol) in anhydrous DMF (15 mL). Degas twice then flush with argon. Keep the flask under argon and heat the reaction at 95°C for 16 h. Dilute with EtOAc then wash with 1N aqueous HCl. Separate the organic layer, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (0:1, 1:9 and 1:4) to give the desired intermediate (448 mg, 68%). MS (ES+) *m/z*: 302 $(M+H)^+$.

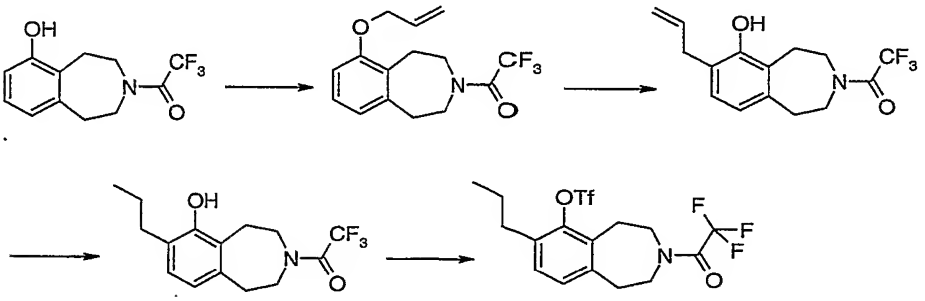
7-Ethyl-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Under nitrogen dissolve 7-acetyl-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.0 g, 3.32 mmol) in anhydrous THF (100 mL). Cool the solution to 0°C, add boron trifluoride diethyl etherate (3.4 mL, 26.6 mmol) and sodium cyanoborohydride (836 mg, 13.3 mmol). Remove the ice bath and stir for 5 h at ambient temperature. Dilute with EtOAc and wash with 0.1N aqueous HCl. Separate the organic layer, dry over Na_2SO_4, filter and concentrate *in vacuo*. MS (ES-) *m/z*: 302 $(M-H)^-$. Mix the residue with trifluoroacetic acid (40 mL) and anhydrous DCM (50 mL) under nitrogen. Cool to 0 °C in an ice bath and add triethyl silane (3.5 mL, 21.9 mmol). After 15 min, remove the ice bath and stir at ambient temperature for 16 h. Concentrate *in*

vacuo and purify by chromatography on silica gel eluting with EtOAc/hexane (1:9) to obtain the desired intermediate (698 mg, 73%). MS (ES-) *m/z*: 286 $(M-H)^-$.

7-Ethyl-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Under nitrogen mix 7-ethyl-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (698 mg, 2.4 mmol), triethylamine (0.67 mL, 4.8 mmol) and anhydrous DCM (25 mL). Cool the mixture in an ice bath, add dropwise trifluoromethanesulfonic anhydride (0.81 mL, 4.8 mmol) and stir at ambient temperature for 3 h. Quench with water and extract three times with DCM. Wash the organic extracts with 0.1N aqueous HCl and brine. Dry over Na_2SO_4, filter and concentrate to obtain the title compound (1.0 g, 100%). MS (ES+) *m/z*: 420 $(M+H)^+$.

Preparation 18

7-Propyl-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



6-Allyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1 g, 3.9 mmol) in acetone (5 mL) and add powdered potassium carbonate (2.8 g, 20 mmol). Add dropwise a solution of allyl bromide (1.04 mL, 12 mmol) in acetone (3 mL) over 10 min and stir at ambient temperature overnight. Filter solids, wash with acetone and concentrate *in vacuo* to give the desired intermediate as an off-white solid (1.15 g, 98%). GC-MS *m/z*: 299 (M^+).

7-Allyl-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 6-allyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.1 g, 3.7 mmol) in DCM (15 mL) and cool to –15 °C. Add 1M boron trichloride in DCM

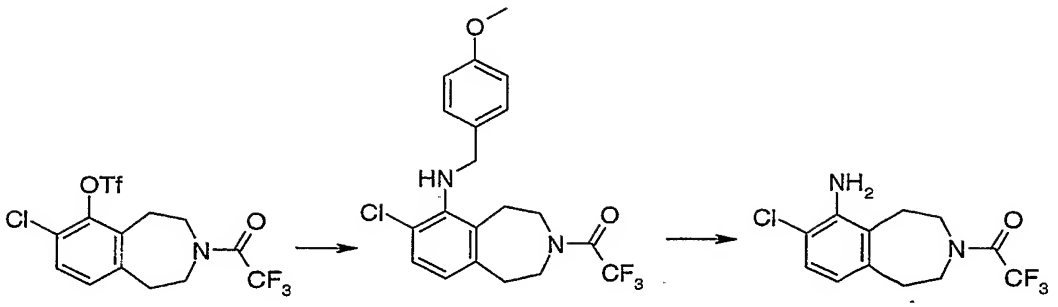
(15 mL, 15 mmol) and warm to ambient temperature. Stir for 30 min at ambient temperature. Add water (50 mL) and extract the aqueous layer three times with DCM. Wash the combined organic extracts with water (100 mL), brine (100 mL), dry over $MgSO_4$, filter, and concentrate *in vacuo* to give the desired intermediate (980 mg, 89%) as a light yellow oil which solidified to an off-white solid upon standing at ambient temperature. MS (ES+) *m/z*: 300 $(M+H)^+$.

6-Hydroxy-7-propyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 7-allyl-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.5 g, 5 mmol) in EtOAc (50 mL) containing 10% Pd/C (1.3 g). Stir at ambient temperature at 1 atm with H_2 (balloon) for 30 min. Filter the catalyst and wash with water (100 mL). Extract the resulting filtrate three times with EtOAc, wash the combined organic extracts with brine, dry over $MgSO_4$, filter and concentrate *in vacuo* to give the desired intermediate as a white solid (1.45 g, 97%). MS (ES+) *m/z*: 302 $(M+H)^+$.

7-Propyl-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Cool a solution of 6-hydroxy-7-propyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (500 mg, 1.9 mmol), triethylamine (390 µL, 2.3 mmol) and DCM (20 mL) in a cryogenic bath set at –35°C and add dropwise over 20 min trifluoromethanesulfonic anhydride (325 µL, 2.3 mmol). Stir at this temperature overnight. Wash the reaction mixture sequentially with water,1N aqueous HCl, water, and brine. Dry the organic layer over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to obtain the title compound as an off-white waxy solid (550 mg, 75%). MS (ES+) *m/z*: 434 $(M+H)^+$.

Preparation 19

6-Amino-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

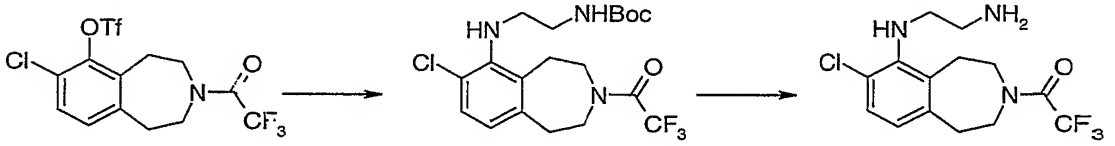


7-Chloro-6-(4-methoxybenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (15 g, 35.3 mmol), with 4-methoxybenzylamine (13.7 mL, 106 mmol) using tris(dibenzylideneacetone)-dipalladium(0) (1.62 g, 1.76 mmol), BINAP (4.40 g, 3.5 mmol) and cesium carbonate (16.1 g, 49.4 mmol) at 80°C for 17 h. Filter the mixture through a pad of Celite® and evaporate the filtrate. Dissolve the residue in DCM and filter through a pad of silica gel. Evaporate the filtrate and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 to 2:3) to give the desired intermediate as a white solid (12.4 g, 86%). MS (ES+) *m/z*: 412 $(M+H)^+$.

6-Amino-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Treat 7-chloro-6-(4-methoxybenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (5.41 g, 13.1 mmol) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (3.59 g, 15.8 mmol) in toluene (66 mL) at ambient temperature for 2 h. Dilute the mixture with EtOAc and wash with saturated aqueous $NaHCO_3$ (5 x 100 mL). Extract the aqueous layer with ether, combine the organic extracts and evaporate to a volume of 300 mL. Extract the organic phase with 1N aqueous HCl (5 x 100 mL), and then wash the combined aqueous layers with ether (4 x 75 mL). Cool the aqueous phase to 0°C, neutralize with 5N aqueous NaOH (100 mL), and extract with DCM (5 x 200 mL). Wash the combined organic extracts with brine, dry over Na_2SO_4 and evaporate to obtain the title compound as a white solid (3.6 g, 94%). MS (ES+) *m/z*: 293 $(M+H)^+$.

Preparation 20

6-(2-Amino-ethylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

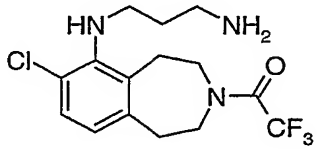


6-(2-*tert*-Butoxycarbonylamino-ethylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to the General Procedure 5-1, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (150 mg, 0.352 mmol), palladium(II) acetate (8 mg, 0.0352 mmol), BINAP (22 mg, 0.0352 mmol), cesium carbonate (163 mg, 0.5 mmol), *t*-butyl *N*-(2-aminoethyl)-carbamate (254 mg, 1.59 mmol) and toluene (6 mL) to give, after chromatography on silica gel eluting with hexane/EtOAc (4:1), the desired intermediate (136 mg, 89%).

6-(2-Amino-ethylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 6-(2-*tert*-butoxycarbonylamino-ethylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (136 mg, 0.31 mmol) in 4M hydrogen chloride in dioxane (20 mL) and stir at ambient temperature for 25 min. Concentrate to afford the hydrochloride salt. Dissolve the salt in DCM and wash with saturated aqueous $NaHCO_3$. Extract the basic aqueous layer with DCM, dry the organic layer over $MgSO_4$, filter, and concentrate *in vacuo* to give the title compound (64 mg, 62%). MS (ES+) *m/z*: 336 $(M+H)^+$.

Preparation 21

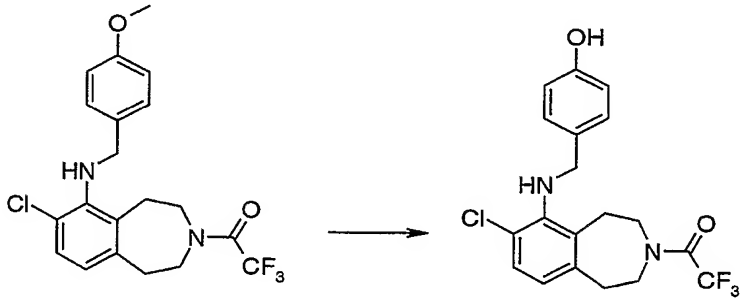
6-(3-Amino-propylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



Use a method similar to the Preparation 20, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (600 mg, 1.41 mmol) and *tert*-butyl *N*-(3-aminopropyl)-carbamate (1.11 g, 6.34 mmol) to give the title compound (34% overall).

Preparation 22

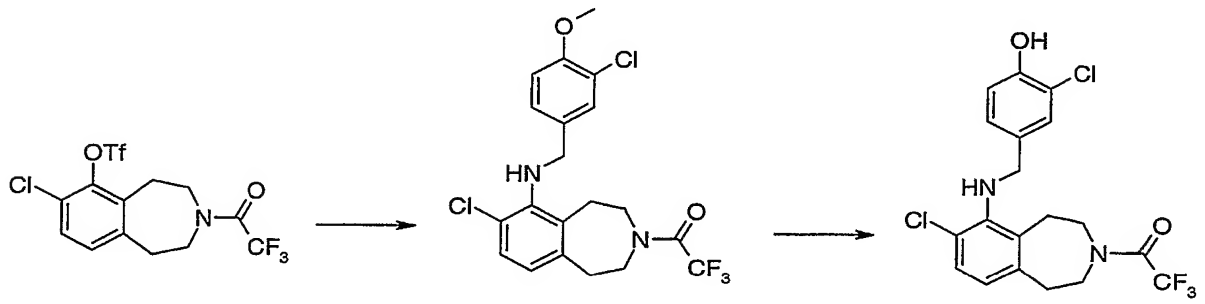
7-Chloro-6-(4-hydroxybenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



Dissolve 7-chloro-6-(4-methoxybenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.667 g) in DCM (40 mL). Add a 1M solution of boron tribromide in DCM (10 mL) at 0°C. Stir the reaction for 12 h and gradually raise to room temperature. Quench the reaction with saturated aqueous $NaHCO_3$ and extract with DCM three times. Combine the organic extracts, wash with brine, dry over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:3) to give the title compound as an oil (888 mg). MS (ES+) *m/z*: 399 $(M+1)^+$.

Preparation 23

7-Chloro-6-(3-chloro-4-hydroxybenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

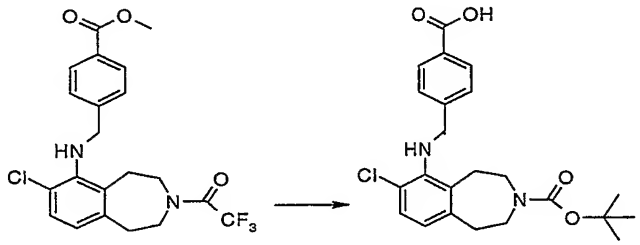


7-Chloro-6-(3-chloro-4-methoxybenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to General Procedure 5-3, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.277 g, 3.0 mmol) and 3-chloro-4-methoxy-benzylamine (669 mg, 3.9 mmol) to give the desired intermediate as a slightly yellow oil (1.554 g, 100%).

7-Chloro-6-(3-chloro-4-hydroxybenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to Preparation 22, using 7-chloro-6-(3-chloro-4-methoxybenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.36 g, 3.0 mmol) to give the title compound as an off-white solid (876 mg, 67% yield). MS (ES+) *m/z*: 433 $(M+H)^+$. MS (ES-) *m/z*: 431 $(M-H)^-$.

Preparation 24

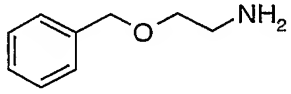
3-(*tert*-Butoxycarbonyl)-6-(4-carboxy-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



Combine 7-chloro-6-(4-methoxycarbonyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.4 g, 0.82 mmol), potassium carbonate (4 g, 28.9 mmol), methanol (3 mL), water (3 mL) and heat at 50°C for 2 h. Cool the reaction mixture to ambient temperature, add saturated aqueous Na_2CO_3 and dilute with DCM (10 mL). Add di-*tert*-butyl-dicarbonate (2.4 g, 10.9 mmol) by portions. Separate the organic layer and extract the aqueous layer with DCM (3 x 10 mL). Combine the organic extracts, dry over anhydrous Na_2SO_4, evaporate the solvent and purify by chromatography on silica gel eluting with DCM and DCM/methanol (9:1) to give the title compound as a white solid (0.3 g, 80%). MS (ES+) *m/z*: 331 $(M+H\text{-Boc})^+$.

Preparation 25

2-Benzyloxyethylamine

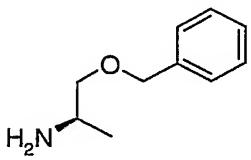


(2-Benzyloxyethyl)-carbamic acid *tert*-butyl ester: Dissolve *tert*-butyl-*N*-(2-hydroxyethyl)-carbamate (10 mL, 64.5 mmol) in anhydrous THF (500 mL) at 0 °C. Add sodium hydride (60% in mineral oil, 3.1 g, 77.4 mmol) and stir for 30 min at 0 °C. Add benzyl bromide (9.2 mL, 77 mmol) followed by tetrabutylammonium iodide (3.7 g, 10 mmol) and stir at ambient temperature overnight. Quench with water (500 mL), extract with diethyl ether (3 x 100 mL), wash the combined organic extracts with brine, dry over $MgSO_4$, filter, and evaporate to give the desired intermediate (15 g), that was used without further purification.

2-Benzyloxyethylamine: Dissolve (2-benzyloxyethyl)-carbamic acid *tert*-butyl ester (15 g) in DCM (50 mL), add trifluoroacetic acid (20 mL) and stir at 0°C for 3 h. Concentrate and dissolve the residue in a minimal amount of DCM. Purify by chromatography on silica gel eluting sequentially with hexane/EtOAc (4:1 and 1:1), EtOAc and 2M ammonia in methanol to give the title compound (8.3 g, 85%).

Preparation 26

(*R*)-2-Benzyloxy-1-methyl-ethylamine



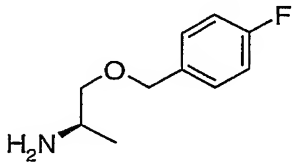
(*R*)-3-Benzyloxy-2-(*tert*-butoxycarbonylamino)-propane: Dissolve (*R*)-(+)-2-(*tert*-butoxycarbonylamino)-1-propanol (875 mg, 5 mmol) in anhydrous THF (50 mL). Add sodium hydride (60% in mineral oil, 210 mg, 5.2 mmol) and stir at 0°C for 30 min. Add benzyl bromide (620 µL, 5.2 mmol) followed by tetrabutylammonium iodide (20 mg, 0.05 mmol) and stir for 3 h at ambient temperature. Pour the mixture into water (200 mL), extract with DCM (3 x 50 mL), wash with brine, dry over $MgSO_4$, filter and concentrate.

Purify by chromatography on silica gel eluting with hexane/EtOAc (19:1) to give the desired intermediate as a colorless oil (800 mg, 60%).

(*R*)-2-Benzyloxy-1-methyl-ethylamine: Dissolve (*R*)-3-benzyloxy-2-(*tert*-butoxycarbonylamino)-propane (800 mg, 3 mmol) in DCM (10 mL), add trifluoroacetic acid (5 mL), and stir at 0 °C for 20 min. Evaporate and purify by SCX chromatography to give the title compound as a colorless oil (440 mg, 89%). MS (ES+) *m/z*: 166 $(M+H)^+$.

Preparation 27

(*R*)-2-(4-Fluorobenzyloxy)-1-methyl-ethylamine

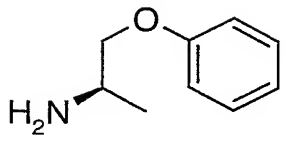


(*R*)-2-(*tert*-Butoxycarbonylamino)-3-(4-fluorobenzyloxy)-propane: Dissolve (*R*)-(+)-2-(*tert*-butoxycarbonylamino)-1-propanol (1.75 mg, 10.5 mmol) in anhydrous THF (50 mL). Add sodium hydride (60% in mineral oil, 480 mg, 12 mmol) and stir at 0°C for 30 min. Add 4-fluorobenzyl bromide (1.5 mL, 12 mmol) followed by tetrabutylammonium iodide (370 mg, 0.1 mmol) and stir for 72 h at ambient temperature. Pour the mixture into water (500 mL), extract with DCM (3 x 150 mL), wash with brine, dry over $MgSO_4$, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the desired intermediate as a yellow oil (2.18 g, 77%).

(*R*)-2-(4-Fluorobenzyloxy)-1-methyl-ethylamine: Dissolve (*R*)-2-(*tert*-butoxycarbonylamino)-3-(4-fluorobenzyloxy)-propane (2.18 g, 7.7 mmol) in DCM (50 mL), add trifluoroacetic acid (25 mL), and stir at 0°C for 20 min. Evaporate and purify by SCX chromatography to give the title compound as a colorless oil (1.2 g, 85%). MS (ES+) *m/z*: 184 $(M+H)^+$.

Preparation 28

(*R*)-1-Methyl-2-phenoxy-ethylamine

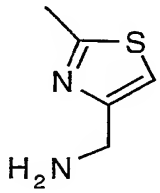


(*R*)-2-(*tert*-Butoxycarbonylamino)-3-phenoxy-propane: Dissolve (*R*)-(+)-2-(*tert*-butoxycarbonylamino)-1-propanol (1.75 g, 10 mmol) and phenol (0.95 g, 10 mmol) in anhydrous THF (75 mL). Cool to 0°C, add triphenylphosphine (4.0 g, 15 mmol) and diisopropylazodicarboxylate dropwise and stir at ambient temperature for 18 h. Pour the mixture into water (300 mL), basify to pH 10 with 5N aqueous NaOH, and extract with ethyl ether (3 x 100 mL). Wash the organic phase with brine, dry over $MgSO_4$, filter and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the desired intermediate as an off-white solid (340 mg, 14%).

(*R*)-1-Methyl-2-phenoxy-ethylamine: Dissolve (*R*)-2-(*tert*-butoxycarbonylamino)-3-phenoxy-propane (340 mg, 1.35 mmol) in DCM (80 mL), add trifluoroacetic acid (35 mL), and stir at 0 °C for 2 h. Evaporate and purify by SCX chromatography to give the title compound as a colorless oil (186 mg, 91%). MS (ES+) *m/z*: 151 $(M+H)^+$.

Preparation 29

4-(Aminomethyl)-2-methyl-thiazole

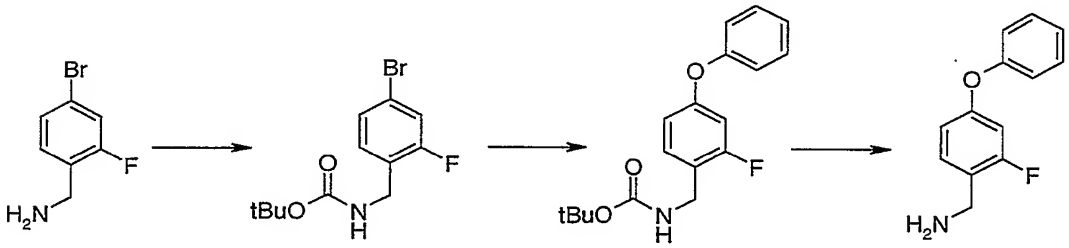


4-(Azidomethyl)-2-methyl-thiazole: Dissolve 4-(chloromethyl)-2-methyl-thiazole (350 mg, 2.37 mmol) and azidotrimethylsilane (315 µL, 2.37 mmol) in anhydrous THF (1 mL) under nitrogen. Add a 1M solution of tetrabutylammonium fluoride (3.6 mL, 3.56 mmol) in THF and stir at ambient temperature overnight. Pour the reaction mixture into water (10 mL), extract with ethyl ether (3 x 2 mL), wash the organic extracts with brine, dry over $MgSO_4$, filter, and evaporate. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the desired intermediate as a colorless oil (165 mg, 45%).

4-(Aminomethyl)-2-methyl-thiazole: Add 4-(azidomethyl)-2-methyl-thiazole (165 mg, 1.07 mmol) to a slurry of methanol containing 10% Pd/C (75 mg) and stir vigorously under 1 atm H_2 for 1 h. Filter, evaporate the solvent, and purify by SCX chromatography to give the title compound (55 mg, 40%).

Preparation 30

2-Fluoro-4-phenoxy-benzylamine



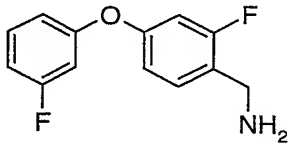
(4-Bromo-2-fluorobenzyl)-carbamic acid *tert*-butyl ester: Mix under nitrogen 4-bromo-2-fluorobenzylamine hydrochloride (7.2 g, 30 mmol), di-*tert*-butyl-dicarbonate (9.8 g, 45 mmol), and potassium carbonate (12.4 g, 90 mmol) in anhydrous THF (200 mL). Stir at ambient temperature for 16 h. Filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to obtain the desired intermediate (6.4 g, 70%). GC-MS *m/z*: 247 $[(M-C_4H_9)^+]$.

(2-Fluoro-4-phenoxy-benzyl)-carbamic acid *tert*-butyl ester: Mix under argon atmosphere (4-bromo-2-fluorobenzyl)-carbamic acid *tert*-butyl ester (2.12 g, 7.0 mmol), phenol (1.32 g, 14 mmol), 2,2,6,6-tetramethylheptane-3,5-dione (129 mg, 0.7 mmol), and cesium carbonate (4.56 g, 14 mmol) in anhydrous NMP (15 mL). Degas the flask, fill with argon and add copper(I) chloride (346 mg, 3.5 mmol) quickly. Degas the flask then fill with argon and heat at 120°C for 5 h. Cool to ambient temperature, dilute with EtOAc and filter. Wash the mixture sequentially with 0.5N aqueous HCl, 0.5N aqueous NaOH and brine. Separate the organic layer, dry over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1 and 3:1) to obtain the desired intermediate (1.28 g, 58%). GC-MS *m/z*: 260 $[(M-C_4H_9)^+]$.

2-Fluoro-4-phenoxy-benzylamine: Dissolve (2-fluoro-4-phenoxy-benzyl)-carbamic acid *tert*-butyl ester (2.44 g, 7.72 mmol) in DCM (200 mL). Add trifluoroacetic acid (50 mL) then stir at ambient temperature for 16 h. Evaporate the solvent, dissolve the residue in DCM and wash with 1N aqueous NaOH. Dry over Na_2SO_4 and concentrate *in vacuo*. Purify by SCX chromatography to obtain the title compound (557 mg, 33%). MS (ES+) *m/z*: 201 $(M+H-NH_3)^+$.

Preparation 31

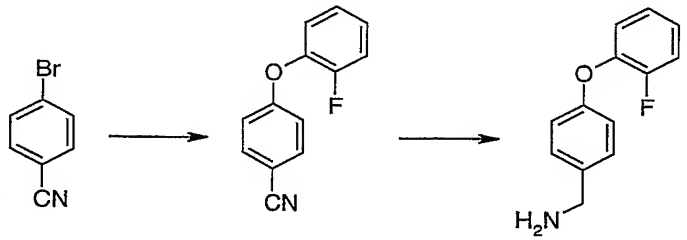
2-Fluoro-4-(3'-fluorophenoxy)-benzylamine



Use a method similar to Preparation 30, using (4-bromo-2-fluorobenzyl)-carbamic acid *tert*-butyl ester (2.12 g, 7.0 mmol) and *m*-fluorophenol (1.57 g, 14 mmol) to give the title compound (468 mg, 47% overall).

Preparation 32

4-(2'-Fluorophenoxy)-benzylamine



4-(2'-Fluorophenoxy)-benzonitrile: Mix under argon atmosphere 4-bromobenzonitrile (2.0 g, 11.3 mmol), 2-fluorophenol (2.5 g, 22.6 mmol), 2,2,6,6-tetramethylheptane-3,5-dione (203 mg, 1.1 mmol), and cesium carbonate (7.4 g, 22.6 mmol) in anhydrous NMP (19 mL). Degas the flask, fill with argon and add copper(I) chloride (554 mg, 5.6 mmol) quickly. Degas the flask then fill with argon and heat at 120°C for 3 h. Cool to ambient temperature, dilute with EtOAc, filter and wash the filtrate sequentially with 2M aqueous HCl, 0.3M aqueous HCl, 2M aqueous NaOH and brine. Separate the organic layer, dry over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting

with hexane/EtOAc (1:0 and 9:1) to obtain the desired intermediate (1.6 g, 66%). MS (ES+) *m/z*: 231 $(M+NH_4)^+$.

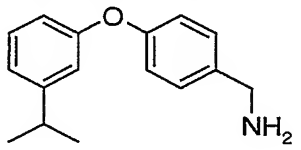
4-(2'-Fluorophenoxy)-benzylamine: Add 4-(2'-fluorophenoxy)-benzonitrile (1.5 g, 7.0 mmol) and ethanol wet Raney® activated nickel (0.4 g) to a Parr pressure vessel. Immediately add a 7N solution of ammonia in methanol (170 mL) and seal the vessel. Purge the reaction vessel with nitrogen, pressurize the reaction mixture with hydrogen (3400 KPa), seal the vessel, agitate the reaction and heat to 60°C. Continue the reaction for 18 h, turn off the heat and allow the reaction mixture to cool to ambient temperature. Vent the excess hydrogen from the vessel and purge the vessel with nitrogen. Filter the reaction mixture to remove the Raney® nickel. Concentrate *in vacuo* and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (9:1) to obtain the title compound (1.2 g, 79%). MS (ES+) *m/z*: 201 $(M+H-NH_3)^+$.

The compound of Preparation 33 may be prepared essentially as described in Preparation 32 using 4-bromobenzonitrile and 3-fluorophenol. Overall yield and MS (ES+) data are shown in the Table below.

Prep.	Compound	Yield (%)	MS (ES+) *m/z*
33	4-(3'-Fluorophenoxy)-benzylamine	53	201 $(M+H-NH_3)^+$

Preparation 34

4-(3'-Isopropylphenoxy)-benzylamine



Use a method similar to Preparation 32 (Step 1), using 4-bromobenzonitrile (2.0 g, 11.3 mmol) and 3-isopropylphenol (3.08 g, 22.6 mmol) to give 4-(3'-isopropylphenoxy)-benzonitrile (885 mg, 33%). MS (ES+) m/z: 255 $(M+NH_4)^+$.

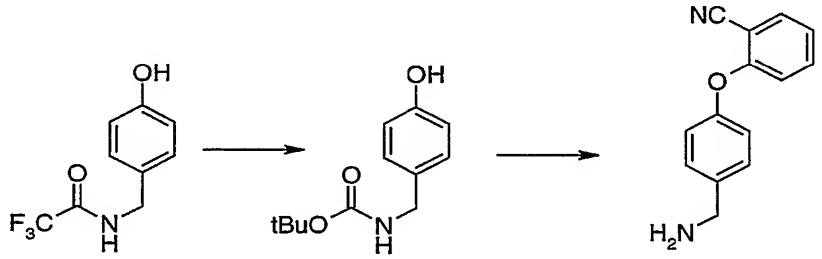
Use a method similar to the reduction procedure described in Preparation 45 (Step 2), using 4-(3'-isopropylphenoxy)-benzonitrile (875 mg, 3.7 mmol) to give the title compound (703 mg, 79%). MS (ES+) m/z: 225 $(M+H-NH_3)^+$.

The compounds of Preparations 35-39 may be prepared essentially as described in Preparation 34 by using 4-bromobenzonitrile and the appropriate phenol. Overall yields and MS (ES+) data are shown in the Table below.

Prep.	Compound	Yield (%)	MS (ES+) *m/z*
35	4-(2'-Isopropylphenoxy)-benzylamine	28	225 $(M+H-NH_3)^+$
36	4-(3'-Methylphenoxy)-benzylamine	60	197 $(M+H-NH_3)^+$
37	4-(2'-Methylphenoxy)-benzylamine	59	197 $(M+H-NH_3)^+$
38	4-(3',5'-Difluorophenoxy)-benzylamine	24	219 $(M+H-NH_3)^+$
39	4-(3'-Chlorophenoxy)-benzylamine	44	217 $(M+H-NH_3)^+$

Preparation 40

2-(4-Aminomethyl-phenoxy)-benzonitrile



(4-Hydroxybenzyl)-carbamic acid *tert*-butyl ester: Mix 2,2,2-trifluoro-*N*-(4-hydroxybenzyl)-acetamide (8.8 g, 40 mmol), and 5N aqueous NaOH (20 mL) in methanol (100 mL). Stir at ambient temperature for 4 h. Adjust pH to about 8 with aqueous HCl. Add solid sodium bicarbonate (4.4 g, 52 mmol), di-*tert*-butyl-dicarbonate (9.3 g, 40 mmol) and DCM. Stir at ambient temperature for 16 h. Dilute with DCM, wash with 1N aqueous HCl and purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 5:5) to obtain the desired intermediate (7.8 g, 87%). MS (ES-) *m/z*: 222 $(M-H)^-$.

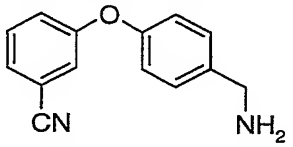
2-(4-Aminomethyl-phenoxy)-benzonitrile: Mix under argon (4-hydroxybenzyl)-carbamic acid *tert*-butyl ester (1.5 g, 6.7 mmol), 2-bromobenzonitrile (813 mg, 4.5 mmol), 2,2,6,6-tetramethylheptane-3,5-dione (83 mg, 0.45 mmol), and cesium carbonate (2.2 g, 6.7 mmol) in anhydrous NMP (8.5 mL). Degas the flask and fill with argon. Add copper(I) chloride (223 mg, 2.25 mmol) quickly. Degas the flask, fill with argon and heat at 120°C for 3 h. Cool to ambient temperature, dilute with EtOAc, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1 and 3:1). Evaporate the solvent and dissolve the residue in DCM (100 mL). Add trifluoroacetic acid (20 mL) and stir at ambient temperature for 16 h. Concentrate *in vacuo,* dissolve the residue in EtOAc and wash with 1N aqueous NaOH. Dry over Na_2SO_4 and concentrate *in vacuo*. Purify by SCX chromatography to obtain the title compound (385 mg, 38%). MS (ES+) *m/z*: 225 $(M+H)^+$.

The compounds of Preparation 41-43 may be prepared essentially as described in Preparation 40 by using (4-hydroxybenzyl)-carbamic acid *tert*-butyl ester (1.5 g, 6.7 mmol) and the appropriate bromide. Overall yields and MS (ES+) data are shown in the Table below.

Prep.	Compound	Yield (%)	MS (ES+) *m/z*
41	4-(2'-Trifluoromethyl-phenoxy)-benzylamine	13	251 $(M+H-NH_3)^+$
42	4-(3'-Trifluoromethyl-phenoxy)-benzylamine	27	251 $(M+H-NH_3)^+$
43	4-(Pyridin-3-yloxy)-benzylamine	11	201 $(M+H)^+$

Preparation 44

3-(4-Aminomethyl-phenoxy)-benzonitrile

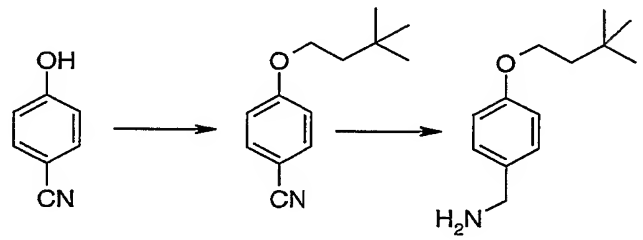


Use a method similar to Preparation 40 (Step 2), using 2,2,2-trifluoro-*N*-(4-hydroxybenzyl)-acetamide (1.0 g, 5.5 mmol) and 3-bromobenzonitrile (673 mg, 3.7

mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 3:1). Concentrate *in vacuo*. Dissolve the residue (287 mg, 0.89 mmol) in methanol (25 mL) and add 5N NaOH (7 mL). Stir at room temperature for 4 h. Dilute with DCM and add solid sodium chloride to the mixture. Extract the aqueous layer three times with DCM. Combine organic extracts, dry over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (94:6) to obtain the title compound (124 mg, 62%). MS (ES+) *m/z*: 500 $(M+H)^+$.

Preparation 45

4-(3,3-Dimethylbutoxy)-benzylamine



4-(3,3-Dimethylbutoxy)-benzonitrile: Mix 4-cyanophenol (1.2 g, 10 mmol), 1-bromo-3,3-dimethylbutane (5.3 g, 32 mmol), powdered potassium carbonate (4.14 g, 30 mmol), and powdered potassium iodide (166 mg, 1 mmol) in acetone (60 mL). Stir under inert atmosphere and heat at reflux for 48 h. Cool the reaction mixture to ambient temperature. Dilute with acetone, filter and evaporate. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) to obtain the desired intermediate (1.8 g, 89%). MS (ES+) *m/z*: 221 $(M+NH_4)^+$.

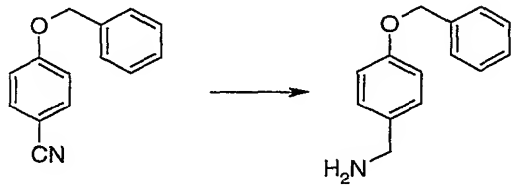
4-(3,3-Dimethylbutoxy)-benzylamine: Mix lithium aluminum hydride (1.0 g, 26.6 mmol) and anhydrous ethyl ether (70 mL) under nitrogen atmosphere. Stir and cool to 0 °C in an ice bath. Add dropwise a solution of 4-(3,3-dimethylbutoxy)-benzonitrile (1.8 g, 8.87 mmol) in anhydrous ethyl ether (20 mL). Stir for 2 h at 0 °C, remove the ice bath and stir at ambient temperature for 18 h. Cool the reaction flask in an ice bath and add carefully dropwise and sequentially water (1 mL), 2N aqueous NaOH (1 mL), and water (2 mL). Stir for 30 min, filter, separate the organic layer, dry over Na_2SO_4 and concentrate *in vacuo* to obtain the title compound (1.62 g, 88%). MS (ES+) *m/z*: 191 $(M+H-NH_3)^+$.

The compounds of Preparations 46-48 may be prepared essentially as described in Preparation 45 by using 4-cyanophenol and the appropriate bromide. Overall yields and MS (ES+) data are shown in the Table below.

Prep.	Compound	Yield (%)	MS (ES+) *m/z*
46	4-Cyclohexylmethoxy-benzylamine	90	203 $(M+H-NH_3)^+$
47	4-(2-Cyclohexylethoxy)-benzylamine	94	217 $(M+H-NH_3)^+$
48	4-(2,2-Dimethylpropoxy)-benzylamine	4	177 $(M+H-NH_3)^+$

Preparation 49

4-Benzyloxy-benzylamine

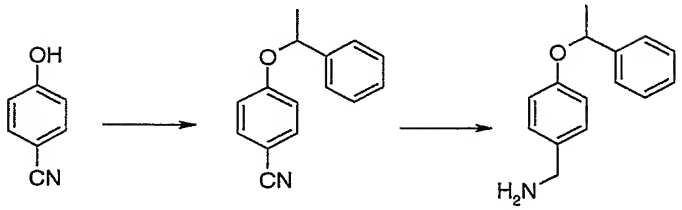


4-Benzyloxy-benzonitrile: Add 4-cyanophenol (1.191 g, 10 mmol), benzyl bromide (1.881 g, 11 mmol), potassium carbonate (3.455 g, 25 mmol) and potassium iodide (166 mg, 1 mmol) to acetonitrile (80 mL) and heat at reflux for 12 h. Cool, partition between EtOAc and water, separate the organic layer, and extract the aqueous layer with EtOAc. Combine the organic extracts, wash with brine, dry over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:6) to give the desired intermediate as a white solid (2.098 g, 100%). MS (ES+) *m/z*: 227 $(M+NH_4)^+$.

4-Benzyloxy-benzylamine: Use a method similar to Preparation 58, using 4-benzyloxy-benzonitrile (2.098 g, 10 mmol), to give the title compound as a white solid (2.021 g, 94%). MS (ES+) *m/z*: 197 $(M+H-NH_3)^+$.

Preparation 50

(±)-4-(1-Phenylethoxy)-benzylamine

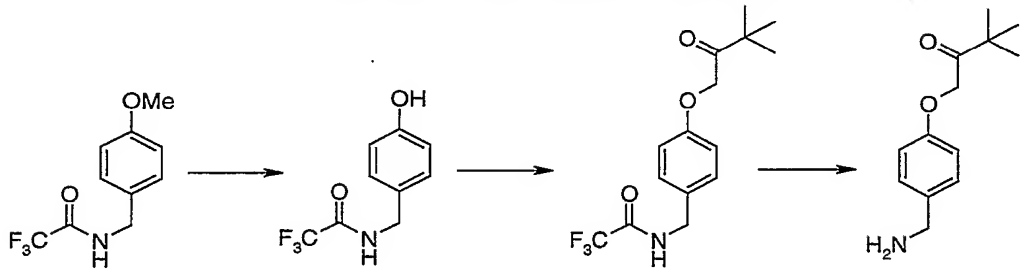


(±)-4-(1-Phenylethoxy)-benzonitrile: Add triphenylphosphine (7.869 g, 30 mmol) to a solution of *sec*-phenylethyl alcohol (1.467 g, 12 mmol), 4-cyanophenol (1.191 g, 10 mmol) and diethyl azodicarboxylate (4.528 g, 26 mmol) in anhydrous THF (50 mL) at 0 °C. Stir the reaction at ambient temperature for 12 h. Dilute with EtOAc, wash with brine, dry over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:8) to give (±)-4-(1-phenylethoxy)-benzonitrile with a small amount of triphenylphosphine (2.49 g total).

(±)-4-(1-Phenylethoxy)-benzylamine: Use a method similar to Preparation 58, using crude (±)-4-(1-phenylethoxy)-benzonitrile, to give the title compound as a colorless oil (1.6 g, 70% two steps). MS (ES+) *m/z*: 211 $(M+H-NH_3)^+$, 455.3 $(2M+H)^+$.

Preparation 51

4-(3,3-Dimethyl-2-oxo-butoxy)-benzylamine



2,2,2-Trifluoro-*N*-(4-methoxybenzyl)-acetamide: Mix under nitrogen atmosphere 4-methoxybenzylamine (13.7 g, 100 mmol) and *N*-methylmorpholine in anhydrous THF (300 mL). Cool to 0°C in an ice bath. Add dropwise a solution of trifluoroacetic anhydride (15.6 mL, 110 mmol) in anhydrous THF (25 mL). Warm up to ambient temperature slowly and stir for 16 h. Concentrate *in vacuo*. Dissolve in EtOAc and wash successively with 1N aqueous NaOH, 1N aqueous HCl, and brine. Separate the organic layer, dry over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel

eluting with hexane/EtOAc (9:1 and 4:1) to obtain the desired intermediate (19 g, 81%). MS (ES-) *m/z*: 232 $(M-H)^-$.

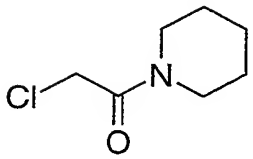
2,2,2-Trifluoro-*N*-(4-hydroxy-benzyl)-acetamide: Dissolve under nitrogen atmosphere 2,2,2-trifluoro-*N*-(4-methoxybenzyl)-acetamide (11.6 g, 50 mmol) in DCM (250 mL). Cool to 0°C in an ice bath. Add dropwise 1M boron tribromide in DCM (100 mL, 100 mmol) and stir for 20 min after addition. Warm to ambient temperature and stir for 16 h. Cool the reaction mixture in an ice bath and quench very carefully with saturated aqueous $NaHCO_3$. Separate the organic layer. Extract the aqueous layer twice with chloroform. Dry the combined organic extracts over Na_2SO_4 and concentrate *in vacuo* to obtain the desired intermediate (8.8 g, 40 mmol). MS (ES-) *m/z*: 218 $(M-H)^-$.

***N*-[4-(3,3-Dimethyl-2-oxo-butoxy)-benzyl]-2,2,2-trifluoroacetamide:**
Mix 2,2,2-trifluoro-*N*-(4-hydroxy-benzyl)-acetamide (438 mg, 2.0 mmol), 1-bromopinacolone (430 mg, 2.4 mmol), anhydrous potassium carbonate (829 mg, 6.0 mmol) and potassium iodide (33 mg, 0.1 mmol) with acetone. Heat under reflux for 12 h. Acidify with 1N aqueous HCl and extract with EtOAc three times. Combine the organic extracts, wash with brine, dry over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:3) to give the desired intermediate as a colorless oil. MS (ES+) *m/z*: 335 $(M+NH_4)^+$. MS (ES-) *m/z*: 316 $(M-H)^-$.

4-(3,3-Dimethyl-2-oxo-butoxy)-benzylamine: Add 5N aqueous NaOH (15 mL) to a solution of *N*-[4-(3,3-dimethyl-2-oxo-butoxy)-benzyl]-2,2,2-trifluoro-acetamide (552 mg, 1.74 mmol) in methanol (10 mL) and stir for 2 h at ambient temperature. Extract the mixture with DCM three times. Dry the combined organic extracts over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (92:8) to give the title compound as a colorless oil (337 mg, 87%). MS (ES+) *m/z*: 205 $(M+H-NH_3)^+$.

Preparation 52

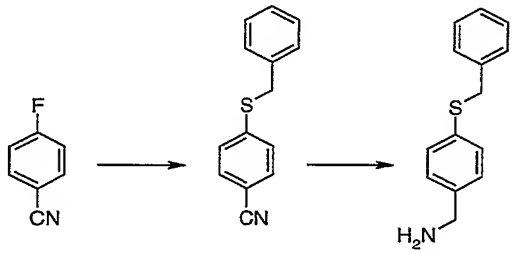
N-(2-Chloro-acetyl)-piperidine



Add chloroacetyl chloride (1.242 g, 11.0 mmol) to a mixture of potassium carbonate (2.073 g, 15 mmol) and piperidine (852 mg, 10 mmol) in THF (50 mL) at 0 °C. Stir the reaction for 12 h and gradually raise to room temperature. Dilute with water, extract with EtOAc three times. Combine the organic extracts and wash sequentially with saturated aqueous $NaHCO_3$, 0.1N aqueous HCl and brine. Dry over Na_2SO_4, filter and concentrate to give the title compound (1.65 g, 100%).

Preparation 53

4-Benzylthio-benzylamine

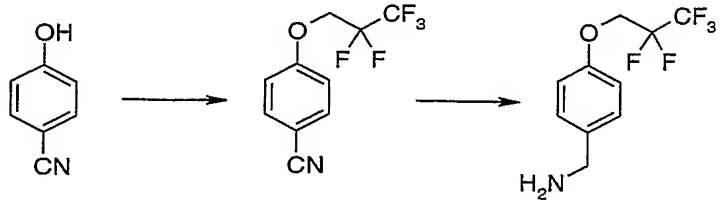


4-Benzylthio-benzonitrile: Mix under argon atmosphere 4-fluorobenzonitrile (1.21 g, 10 mmol), benzyl mercaptan (1.86 g, 15 mmol), and cesium carbonate (6.5 g, 20 mmol) in anhydrous NMP (20 mL). Degas the flask and fill with argon. Heat at 120°C for 3 h. Cool to ambient temperature, dilute with EtOAc, filter and wash with 1N aqueous HCl. Separate the organic layer, dry over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) to obtain the desired intermediate (689 mg, 31%). GC-MS *m/z*: 225 (M^+).

4-Benzylthio-benzylamine: Use the reduction procedure described in Preparation 45 (Step 2), using 4-benzylthio-benzonitrile (689 mg, 3.1 mmol) to give, after SCX chromatography, the title compound (464 mg, 64%). MS (ES+) *m/z*: 213 $(M+H-NH_3)^+$.

Preparation 54

4-(2,2,3,3,3-Pentafluoropropoxy)-benzylamine

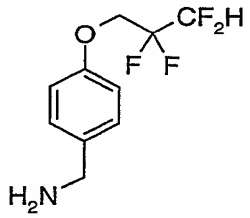


4-(2,2,3,3,3-Pentafluoropropoxy)-benzonitrile: Heat a mixture of 4-hydroxy-benzonitrile potassium fluoride complex (3.0 g, 16.9 mmol) and 1,1,1,2,2-pentafluoro-3-iodo-propane (10.8 g, 37.2 mmol) in DMSO (80 mL) to 130°C for 20 h. Cool the mixture to ambient temperature, dilute with hexane/EtOAc (1:1, 200 mL) and wash with aqueous 10% NaCl (3 x 50 mL). Dry the organic layer, concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (10:1, 10:2 and 10:3) to obtain the desired intermediate (1.1 g, 26%). GC-MS *m/z*: 251 (M^+).

4-(2,2,3,3,3-Pentafluoropropoxy)-benzylamine: Use a method similar to the General Procedure 6-4, using 4-(2,2,3,3,3-pentafluoropropoxy)-benzonitrile (1.1 g, 4.1 mmol), to obtain the title compound (1.1 g, 99%). GC-MS *m/z*: 254 (M^+-H).

Preparation 55

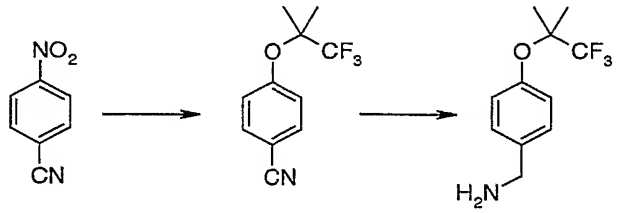
4-(2,2,3,3-Tetrafluoropropoxy)-benzylamine



Use a method similar to Preparation 54, using 4-hydroxy-benzonitrile potassium fluoride complex (4.2 g, 23.7 mmol) and 1,1,2,2-tetrafluoro-3-iodo-propane (10 g, 41.3 mmol), to give the title compound (38% overall). GC-MS *m/z*: 236 (M^+-H).

Preparation 56

4-(2,2,2-Trifluoro-1,1-dimethyl-ethoxy)-benzylamine

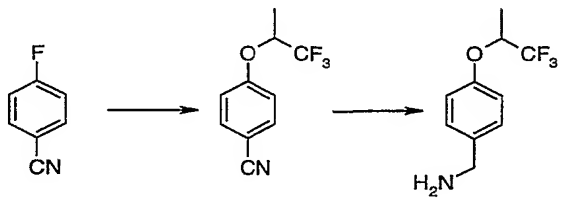


4-(2,2,2-Trifluoro-1,1-dimethyl-ethoxy)-benzonitrile: Add 2-trifluoromethyl-2-propanol (3.4 g, 27 mmol) slowly to a slurry of sodium hydride (0.6 g, 60% in mineral oil, washed with hexane) in HMPA (5 mL) under nitrogen. Stir the slurry for 15 min and add a solution of 4-nitrobenzonitrile (2.0 g, 13.5 mmol) in HMPA (10 mL). Stir the resulting purple slurry at ambient temperature for 16 h, dilute with diethyl ether (100 mL) and wash with 5% aqueous HCl (30 mL). Separate the layers and extract the aqueous layer with diethyl ether (2 x 50 mL). Combine the organic extracts and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 1:1) to obtain the desired intermediate (780 mg, 25%). GC-MS *m/z*: 229 (M^+).

4-(2,2,2-Trifluoro-1,1-dimethyl-ethoxy)-benzylamine: Use a method similar to the General Procedure 6-4 to reduce 4-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-benzonitrile (780 mg, 3.4 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (40:1, 20:1 and 10:1) to obtain the title compound (780 mg, 98%). GC-MS *m/z*: 232 (M^+-H).

Preparation 57

(±)-4-(2,2,2-Trifluoro-1-methyl-ethoxy)-benzylamine



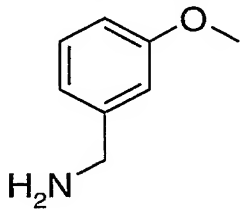
(±)-4-(2,2,2-Trifluoro-1-methyl-ethoxy)-benzonitrile: Add 1,1,1-trifluoro-2-propanol (3.8 g, 66 mmol) slowly to a slurry of sodium hydride (730 mg, 60% in mineral oil, washed with hexane) in HMPA (5 mL) under nitrogen. Stir the slurry for 15 min and add

4-fluorobenzonitrile (2 g, 16.5 mmol). Heat the slurry in a sealed flask to 90°C for 16 h. Cool the mixture to ambient temperature and pour the mixture into a flask containing 5% aqueous HCl (20 mL). Extract the mixture with diethyl ether (3 x 50 mL), and wash with 5% aqueous HCl (25 mL). Dry the organic layer over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to obtain the desired intermediate (2.5 g, 70%). GC-MS *m/z*: 215 (M^+).

(±)-4-(2,2,2-Trifluoro-1-methyl-ethoxy)-benzylamine: Use a method similar to the General Procedure 6-4, using (±)-4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzonitrile (1.0 g, 4.6 mmol), to obtain the title compound (1.1 g, 95%). GC-MS *m/z*: 218 (M^+-H).

Preparation 58

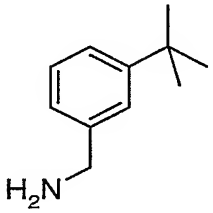
3-Methoxybenzylamine



Add lithium aluminum hydride (3.795 g, 100 mmol) portion wise to a solution of 3-methoxybenzonitrile (5.326 g, 40 mmol) in anhydrous ethyl ether (200 mL) at 0°C. Stir for 1 h, warm to ambient temperature and continue to stir for 12 h. Quench the reaction with 0.1N aqueous NaOH, filter the solid, dry the filtrate over Na_2SO_4 and concentrate to give the title compound as a colorless oil (5.107 g, 93%). MS (ES+) *m/z*: 138 $(M+H)^+$.

Preparation 59

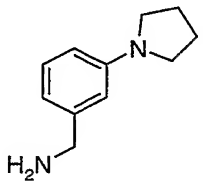
3-(*tert*-Butyl)benzylamine



Dissolve 3-*tert*-butyltoluene (0.5 mL, 2.9 mmol) in carbon tetrachloride (20 mL). Add NBS (530 mg, 3 mmol) and irradiate the reaction mixture with a 250 watt sun-lamp with simultaneous heating to reflux for 1 h. Cool to ambient temperature, filter, and concentrate filtrate to dryness to give crude 1-bromomethyl-3-*tert*-butylbenzene. Dissolve crude 1-bromomethyl-3-*tert*-butylbenzene (600 mg) in anhydrous DMF. Add portion wise sodium azide (260 mg, 4 mmol) and stir at room temperature for 2 h. Pour the mixture into water (250 mL), extract with EtOAc (3x50 mL), wash combined organic extracts with brine, dry over $MgSO_4$, filter and evaporate solvent to give crude 1-azidomethyl-3-*tert*-butylbenzene, that was used without further purification. Dissolve crude 1-azidomethyl-3-*tert*-butylbenzene in methanol containing 10% Pd/C (75 mg) at 5°C, and stir the resulting slurry under 1 atm H_2 for 1 h. Filtrate, concentrate *in vacuo* and purify by chromatography on silica gel eluting sequentially with hexane/EtOAc (4:1 and 1:1), EtOAc, methanol and 2M ammonia in methanol to give the title compound (255 mg, 53% overall). MS (ES+) *m/z*: 164 $(M+H)^+$.

Preparation 60

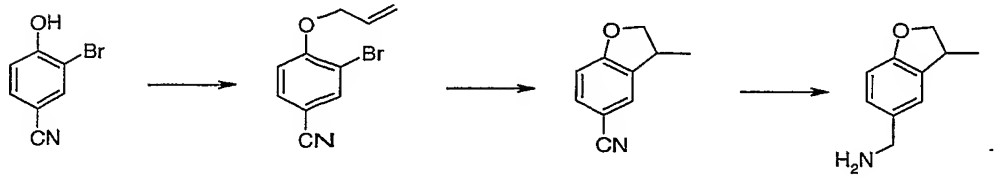
(3-Pyrrolidin-1-yl)benzylamine



Slurry a mixture of (3-bromobenzyl)-carbamic acid *tert*-butyl ester (600 mg, 2.1 mmol, U.S. Pat. Appl. Publ. US 2003134885), pyrrolidine (450 mL, 5.2 mmol), tris(dibenzylideneacetone)dipalladium(0) (200 mg, 0.21 mmol), BINAP (400 mg, 0.63 mmol) and cesium carbonate (960 mg, 2.94 mmol) in anhydrous toluene (10 mL). Degas under vacuum, fill the system with nitrogen and heat in a sealed flask at 90 °C for 18 h. Cool to room temperature, dilute with diethyl ether, filter, and concentrate *in vacuo*. Dissolve the resulting residue in DCM (10 mL) and add trifluoroacetic acid (5 mL). Stir at ambient temperature for 1 h and concentrate *in vacuo*. Purify by chromatography on silica gel eluting sequentially with hexane/EtOAc (1:1), EtOAc and 2M ammonia in methanol. Purify again by SCX chromatography to give the title compound as a brown oil (300 mg, 85% overall). MS (ES+) *m/z*: 178 $(M+H)^+$.

Preparation 61

(±)-*C*-(3-Methyl-2,3-dihydro-benzofuran-5-yl)-methylamine

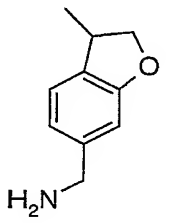
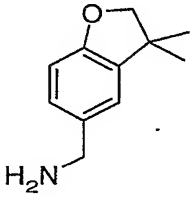
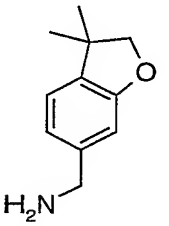


4-Allyloxy-3-bromo-benzonitrile: Mix 3-bromo-4-hydroxy-benzonitrile (1.520 g, 8.0 mmol), allyl bromide (1.161 g, 9.6 mmol), potassium carbonate (3.317 g, 24 mmol) and potassium iodide (133 mg, 0.1 mmol) in acetone (80 mL). Heat the mixture to reflux for 12 h. Cool to ambient temperature, add EtOAc, wash the organic layer with water, and extract the aqueous layer twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:8) to obtain the desired intermediate.

(±)-3-Methyl-2,3-dihydro-benzofuran-5-carbonitrile: Add tri-*n*-butyltin hydride (5.821 g, 20 mmol) and AIBN (411 mg, 2.5 mmol) to a solution of 4-allyloxy-3-bromo-benzonitrile (595 mg, 2.5 mmol). Heat the reaction at reflux for 20 h. Dilute with EtOAc and wash with water. Extract the aqueous layer with EtOAc three times. Combine the organic extracts, wash with brine, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:8) to give the desired intermediate as a white solid (474 mg, 100% with a trace amount of tributyltin derivative).

(±)-*C*-(3-Methyl-2,3-dihydro-benzofuran-5-yl)-methylamine: Use a method similar to Preparation 58, using (±)-3-methyl-2,3-dihydro-benzofuran-5-carbonitrile (474 mg, 2.98 mmol) to give the title compound as a colorless oil (410 mg, 84%).

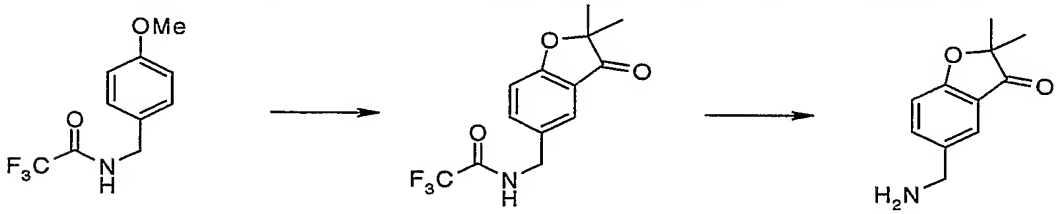
The compounds of Preparations 62-64 may be prepared essentially as described in Preparation 61 by using 3-bromo-4-hydroxy-benzonitrile or 4-bromo-3-hydroxy-benzonitrile and the appropriately substituted allyl bromide. MS (ES+) data are shown in the Table below.

Prep.	Structure	Compound	MS (ES+) *m/z*
62		(±)-*C*-(3-Methyl-2,3-dihydro-benzofuran-6-yl)-methylamine	164 $(M+H)^+$
63		C-(3,3-Dimethyl-2,3-dihydro-benzofuran-5-yl)-methylamine	ND
64		*C*-(3,3-Dimethyl-2,3-dihydro-benzofuran-6-yl)-methylamine	178 $(M+H)^+$

ND= Not determined

Preparation 65

C-(2,2-Dimethyl-3-oxo-2,3-dihydro-benzofuran-5-yl)-methylamine



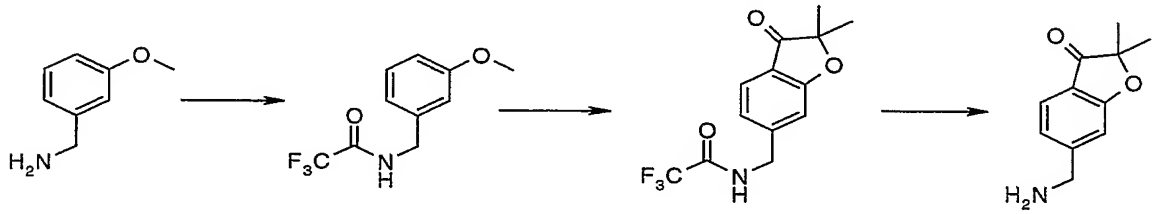
***N*-(2,2-Dimethyl-3-oxo-2,3-dihydro-benzofuran-5-ylmethyl)-2,2,2-trifluoro-acetamide:** Add 2-bromoisobutyryl bromide (1.724 g, 7.5 mmol) to a solution of 2,2,2-trifluoro-*N*-(4-methoxy-benzyl)-acetamide (1.166 g, 5.0 mmol) in 1,2-dichloroethane (8 mL) at 15°C, then add powdered anhydrous iron(III) chloride (973 mg, 6.0 mmol). Stir the reaction at 15°C for 3 h and at ambient temperature for 8 days. Add dropwise saturated aqueous potassium sodium tartrate, then water and EtOAc, and stir for 1 h. Filter off the solid, separate the organic layer, and extract the aqueous layer three times

with EtOAc. Combine the organic extracts, wash with brine, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:3) to give the desired intermediate (253 mg, 17%).

***C*-(2,2-dimethyl-3-oxo-2,3-dihydro-benzofuran-5-yl)-methylamine:** Dissolve *N*-(2,2-dimethyl-3-oxo-2,3-dihydro-benzofuran-5-ylmethyl)-2,2,2-trifluoro-acetamide (253 mg, 0.88 mmol) in 7M ammonia in methanol and stir at ambient temperature for 5 days. Remove volatiles *in vacuo*, purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (92:8) to give the title compound (44 mg, 26%). MS (ES+) *m/z*: 175 $(M+H-NH_3)^+$.

Preparation 66

C-(2,2-Dimethyl-3-oxo-2,3-dihydro-benzofuran-6-yl)-methylamine

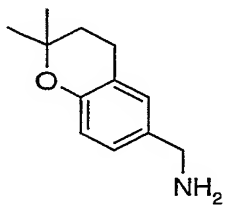


2,2,2-Trifluoro-*N*-(3-methoxy-benzyl)-acetamide: Add trifluoroacetic anhydride (6.3 g, 30 mmol) to a solution of 3-methoxybenzylamine (3.43 g, 25 mmol) and *N*-methyl-morpholine (3.793 g, 37.5 mmol) in THF (80 mL) at 0°C and stir at this temperature for 4 h. Warm to ambient temperature and stir for 12 h. Dilute with EtOAc, wash sequentially with water, 1N aqueous HCl, saturated aqueous $NaHCO_3$ and brine. Dry the organic layer over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:3) to give the desired intermediate (5.344 g, 91%).

***C*-(2,2-Dimethyl-3-oxo-2,3-dihydro-benzofuran-6-yl)-methylamine:** Use a method similar to Preparation 65, using 2,2,2-trifluoro-*N*-(3-methoxy-benzyl)-acetamide (1.166 g, 5 mmol), to give the title compound (220 mg, 23% two steps). MS (ES+) *m/z*: 192 $(M+H)^+$.

Preparation 67

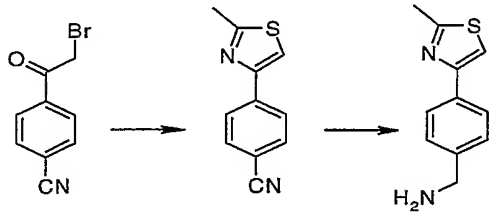
6-Aminomethyl-2,2-dimethyl-2*H*-chromene



Add 2,2-dimethyl-2*H*-chromene-6-carbonitrile (1.5 g, 8.1 mmol) and ethanol wet Raney® activated nickel (0.4 g) to a Parr pressure vessel. Immediately add 7N ammonia in methanol (170 mL) and seal the vessel. Purge the reaction vessel with nitrogen, pressurize the reaction mixture with hydrogen (3400 KPa), seal the vessel, agitate the reaction and heat to 60°C for 20 h. Turn off the heat and allow the reaction mixture to cool to ambient temperature. Vent the excess hydrogen from the vessel and purge the vessel with nitrogen. Filter the reaction mixture to remove the Raney® nickel. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (9:1) to obtain the title compound (1.5 g, 97%). MS (ES+) *m/z*: 175 $(M+H-NH_3)^+$.

Preparation 68

4-(2-Methylthiazol-4-yl)-benzylamine

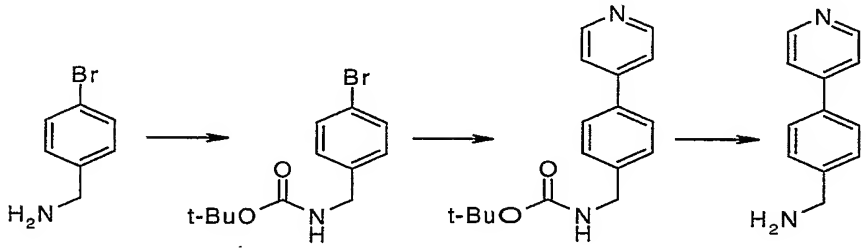


4-(2-Methylthiazol-4-yl)-benzonitrile: Suspend 4-cyanophenacyl bromide (515 mg, 2.23 mmol) in ethanol (15 mL). Add thioacetamide (171 mg, 2.23 mmol) and sodium bicarbonate (187 mg, 2.23 mmol) and heat the mixture under reflux for 2 h. Concentrate *in vacuo* and dissolve the residue in DCM. Wash the organic fraction with water, dry over Na_2SO_4, filter and concentrate to give a solid. Suspend the solid in ether/hexane and filter under vacuum washing with hexane to obtain the desired intermediate as a white solid (415 mg, 93%). GC-MS *m/z*: 200 (M^+).

4-(2-Methylthiazol-4-yl)-benzylamine: Dissolve 4-(2-methylthiazol-4-yl)-benzonitrile (305 mg, 1.52 mmol) in anhydrous THF (50 mL). Add a 1M solution of lithium aluminum hydride in THF (3.05 mL, 3.05 mmol). Heat the mixture overnight under reflux. Cool the reaction mixture with ice/water and work-up sequentially with EtOAc and water. Filter the mixture over Celite®. Separate the organic phase, and extract the aqueous phase with chloroform. Dry the combined organic extracts over Na_2SO_4, filter and concentrate to obtain the title compound as an oil (120 mg) that was used without further purification. GC-MS *m/z*: 204 (M^+).

Preparation 69

4-(Pyridin-4-yl)-benzylamine



***N*-(*tert*-Butoxycarbonyl)-4-bromo-benzylamine:** Add di-*tert*-butyl-dicarbonate (1.173 g, 5.375 mmol) and triethylamine (1.087 g, 1.0 mL, 10.75 mmol) to a stirred solution of 4-bromobenzylamine (1.0 g, 5.375 mmol) in anhydrous DCM (15 mL). Stir overnight at ambient temperature, dilute with DCM and wash with water. Separate the organic phase, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 19:1 and 9:1) to obtain the desired intermediate as a solid (1.24 g, 81%).

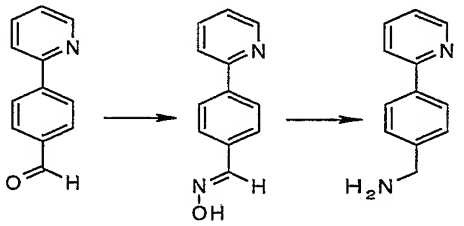
***N*-(*tert*-Butoxycarbonyl)-4-(pyridin-4-yl)-benzylamine:** Dissolve *N*-(*tert*-butoxycarbonyl)-4-bromo-benzylamine (0.8 g, 2.807 mmol) in anhydrous DME (12 mL) under nitrogen. Add tetrakis(triphenylphosphine)palladium(0) (0.162 g, 0.14 mmol), pyridine-4-boronic acid (0.513 g, 4.211 mmol), and a 2M aqueous Na_2CO_3 solution (2.8 mL, 5.614 mmol). Heat the reaction overnight at 70°C. Cool the mixture to ambient temperature, dilute with EtOAc, and filter over Celite®. Wash the organic fraction with water, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on

silica gel eluting with hexane/EtOAc (1:0, 4:1 and 1:1) to give the title compound as an oil (0.295 g, 37%). GC-MS *m/z*: 284 (M^+).

4-(Pyridin-4-yl)-benzylamine: Dissolve *N*-(*tert*-butoxycarbonyl)-4-(4-pyridyl)-benzylamine (363 mg, 1.276 mmol) in anhydrous DCM (10 mL). Add 4N hydrogen chloride in dioxane (10 mL) and stir overnight at ambient temperature. Concentrate *in vacuo* to obtain the hydrochloride salt in pure form as a solid. Dissolve the solid in saturated aqueous $NaHCO_3$ and extract three times with DCM and three more times with EtOAc. Combine the organic extracts, dry over Na_2SO_4, filter and concentrate to obtain the title compound as a solid (166 mg, 71 %). GC-MS *m/z*: 184 (M^+).

Preparation 70

4-(Pyridin-2-yl)-benzylamine



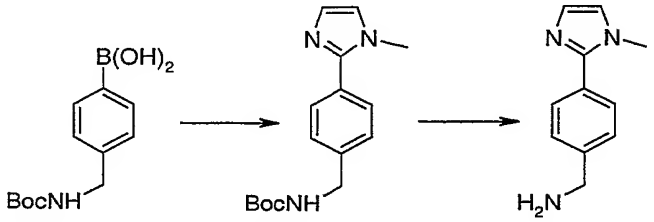
4-(2-Pyridyl)-benzaldehyde oxime: Add hydroxylamine hydrochloride (0.379 g, 5.458 mmol) and a solution of NaOH (0.327 g, 8.187 mmol) in water (2 mL) to a solution of 4-(2-pyridyl)-benzaldehyde (0.5 g, 2.729 mmol) in ethanol (10 mL). Heat the mixture at 80 °C for 2 h. Cool to ambient temperature and remove the solvent *in vacuo*. Partition the residue between EtOAc and water. Separate and dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 4:1) to obtain the desired intermediate (311 mg, 58%). GC-MS *m/z*: 198 (M^+).

4-(Pyridin-2-yl)-benzylamine: Add Pd/C (10%, 50 mg) and concentrated HCl (2 mL) to a solution of 4-(2-pyridyl)-benzaldehyde oxime (0.29 g, 1.46 mmol) in absolute ethanol (20 mL). Hydrogenate the mixture at 50 psi for 2 h. Filter over Celite®, wash with ethanol and concentrate *in vacuo* to obtain the hydrochloride salt in pure form as a solid. Dissolve the solid in saturated aqueous $NaHCO_3$, extract the aqueous solution three times

with DCM and three more times with EtOAc. Combine the organic extracts, dry over Na_2SO_4, filter and concentrate *in vacuo* to obtain the title compound as a solid (130 mg, 48 %). GC-MS *m/z*: 184 (M^+).

Preparation 71

4-(1-Methyl-1*H*-imidazol-2-yl)-benzylamine

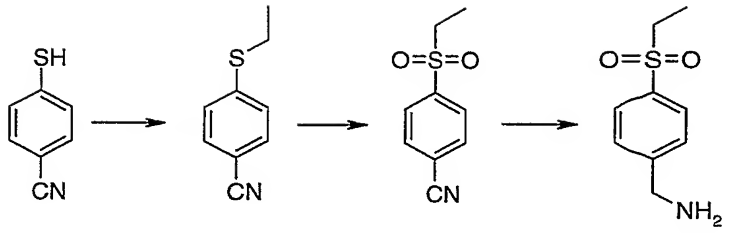


[4-(1-Methyl-1*H*-imidazol-2-yl)-benzyl]-carbamic acid *tert*-butyl ester: Add 4-(*N*-*tert*-Butoxycarbonyl-aminomethyl)phenylboronic acid (1.9 g, 7.4 mmol), 2-bromo-1-methyl-1*H*-imidazole (800 mg, 5.0 mmol), tetrakis(triphenylphosphine)-palladium(0) (287 mg, 0.25 mmol) and potassium carbonate (860 mg, 6.2 mmol) to a flask containing toluene (10 mL). Heat the mixture in a sealed flask at 90°C for 16 h. Cool the mixture, dilute with EtOAc (50 mL), filter through Celite®, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc/methanol (49:50:1) to obtain the desired intermediate (1.2 g, 83%). GC-MS *m/z*: 287(M^+).

4-(1-Methyl-1*H*-imidazol-2-yl)-benzylamine: Dissolve [4-(1-methyl-1*H*-imidazol-2-yl)-benzyl]-carbamic acid *tert*-butyl ester (500 mg, 1.7 mmol) in DCM (20 mL) and trifluoroacetic acid (5 mL). Stir the mixture for 1 h at ambient temperature. Concentrate *in vacuo* and purify by SCX chromatography to obtain the title compound (240 mg, 74%). MS (ES+) *m/z*: 188 $(M+H)^+$.

Preparation 72

4-Ethanesulfonyl-benzylamine



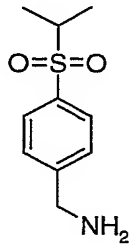
4-Ethylthio-benzonitrile: Combine 4-mercapto-benzonitrile (0.4 g, 2.96 mmol), bromoethane (1.4 mL, 8.88 mmol) and potassium carbonate (3.3 g, 23.7 mmol) in anhydrous DMF (7 mL) and heat at 60°C for 17 h. Cool the reaction mixture to ambient temperature and partition between brine (20 mL) and EtOAc (20 mL). Separate the organic layer, dry over anhydrous Na_2SO_4 and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1 and 4:1) to obtain the desired intermediate as a colorless oil (0.4 g, 83%).

4-Ethanesulfonyl-benzonitrile: Dissolve 4-ethylthio-benzonitrile (0.4 g, 2.4 mmol) in TFA (10 mL) and add slowly hydrogen peroxide (30 w%, 10 mL) at 5 °C. Stir the reaction mixture at ambient temperature for 2 h and partition between brine (20 mL) and DCM (20 mL). Separate the organic layer, dry over anhydrous Na_2SO_4 and concentrate to obtain the desired intermediate as a white solid (0.5 g, 100%). GC-MS *m/z*: 195 (M^+).

4-Ethanesulfonyl-benzylamine: Combine 4-ethanesulfonyl-benzonitrile (0.7 g, 3.5 mmol), Raney® 3201 nickel (slurry in water, 0.1 g), 2N ammonia in methanol (20 mL) and hydrogenate at 50 psi for 17 h. Filter the reaction mixture through a pad of Celite® and concentrate *in vacuo*. Purify by SCX chromatography to obtain the title compound as a yellow oil (0.3 g, 43%).

Preparation 73

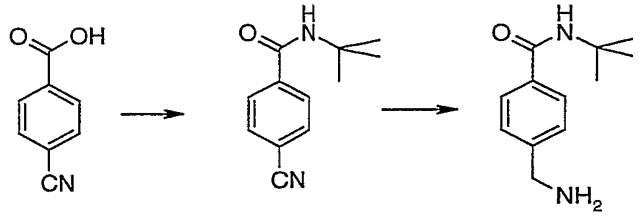
4-(2-Propanesulfonyl)-benzylamine



Use a method similar to Preparation 72, using 4-mercapto-benzonitrile (0.5 g, 3.7 mmol) and 2- bromopropane (1.4 g, 11.38 mmol), to obtain the title compound as a yellow oil (0.3 g, 39% overall).

Preparation 74

4-Aminometyl-*N-tert*-butyl-benzamide

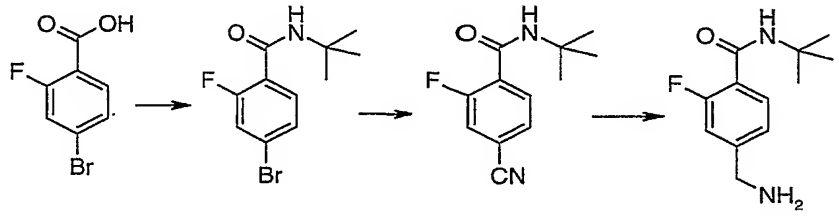


***N-tert*-butyl-4-cyano-benzamide:** Combine 4-cyanobenzoic acid (30 mg, 2.07 mmol), *tert*-butylamine (0.5 mL, 4.13 mmol), triethylamine (0.4 mL, 2.89 mmol), and HATU (1.1 g, 2.89 mmol) in anhydrous DMF (7 mL). Stir at ambient temperature for 17 h. Partition the reaction mixture between brine (15 mL) and diethyl ether (15 mL), separate the organic layer, dry over anhydrous Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with DCM to obtain the desired intermediate as a white solid (0.4 g, 89%). MS (ES+) *m/z*: 203 $(M+H)^+$.

4-Aminometyl-*N-tert*-butyl-benzamide: Combine *N-tert*-butyl-4-cyano-benzamide (0.4 g, 1.78 mmol), Raney® 3201 nickel (slurry in water, 0.03 g), 2N ammonia in methanol (20 mL) and hydrogenate at 50 psi for 1 h. Filter the reaction mixture through a pad of Celite®, remove the solvent and purify by SCX chromatography to obtain the title compound as a colorless oil (0.4 g, 95%). MS (ES+) *m/z*: 207 $(M+H)^+$.

Preparation 75

4-Aminometyl-2-fluoro-*N-tert*-butyl-benzamide



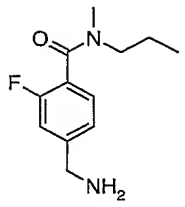
4-Bromo-*N*-*tert*-butyl-2-fluoro-benzamide: Combine 4-bromo-2-fluoro-benzoic acid (5.0 g, 22.83 mmol), thionyl chloride (10 mL, 0.137 mol) in toluene (10 mL) and reflux for 2 h. Evaporate the reaction mixture to obtain 4-bromo-2-fluoro-benzoyl chloride (5.0 g, 93%) and use for the next step without further purification. Dissolve *tert*-butylamine (0.8 mL, 5.12 mmol) and triethylamine (0.8 mL, 6.32 mmol) in anhydrous DCM (20 mL), cool to 0°C and add a solution of 4-bromo-2-fluoro-benzoyl chloride (1.0 g, 4.22 mmol) in anhydrous DCM (10 mL). Stir the reaction mixture at 0°C for 10 min, warm to ambient temperature and continue to stir for 30 min. Wash the reaction mixture with brine (2 x 10 mL), dry the organic extracts over anhydrous Na_2SO_4, evaporate the solvent and purify by chromatography on silica gel eluting with DCM to obtain the desired intermediate as a white solid (1.0 g, 87%). MS (ES+) *m/z*: 275 $(M+H)^+$.

***N*-*tert*-Butyl-4-cyano-2-fluoro-benzamide:** Combine 4-bromo-*N*-*tert*-butyl-2-fluoro-benzamide (1.0 g, 3.65 mmol) and copper(I) cyanide (0.7 g, 7.29 mmol) in anhydrous DMF (10 mL) and reflux for 17 h. Cool the reaction mixture to ambient temperature and treat with 50% (v/v) aqueous ethylenediamine (20 mL). Extract the reaction mixture with diethyl ether (3 x 10 mL), combine the organic extracts, wash with brine (2 x 10 mL) and dry the organic layer over Na_2SO_4. Evaporate the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1, 4:1, 7:3 and 3:2) to obtain the desired intermediate as a white solid (0.6 g, 77%). MS (ES+) *m/z*: 221 $(M+H)^+$.

4-Aminomethyl-2-fluoro-*N*-*tert*-butyl-benzamide: Combine *N*-*tert*-butyl-4-cyano-2-fluoro-benzamide (0.6 g, 1.78 mmol), Raney® 3201 nickel (slurry in water, 30 mg), 2N ammonia in methanol (30 mL) and hydrogenate at 50 psi for 1 h. Filter the reaction mixture through a pad of Celite®, concentrate *in vacuo* and purify by SCX chromatography to obtain the title compound as a colorless oil (0.6 g, 96%).

Preparation 76

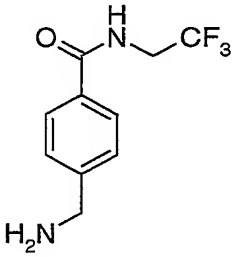
4-Aminometyl-2-fluoro-*N*-methyl-*N*-propyl-benzamide



Use a method similar to Preparation 75, using 4-bromo-2-fluoro-benzoic acid (1.0 g, 4.56 mmol) and *N*-methyl-propylamine (0.5 mL, 5.05 mmol), to give the title compound as a colorless oil (0.5 g, 49%). GC-MS *m/z*: 224 (M^+).

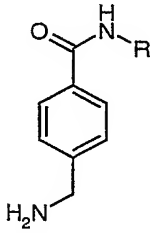
Preparation 77

4-Aminomethyl-*N*-(2,2,2-trifluoro-ethyl)-benzamide

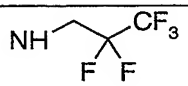
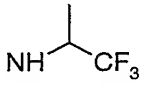
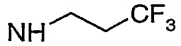
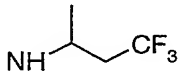
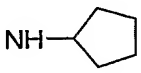
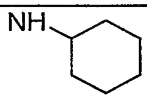
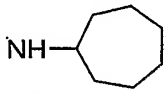
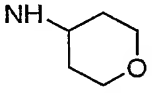
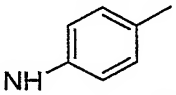
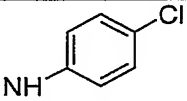
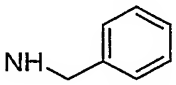
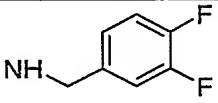
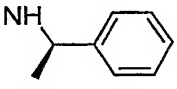
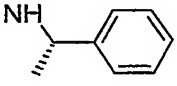
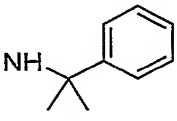


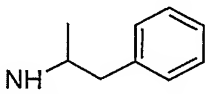
Use the General Procedure 6-1, using 2,2,2-trifluoroethylamine (197 mg, 2 mmol) and 4-(*tert*-butoxycabonylamino-methyl)-benzoic acid, to give the title compound as a clear oil (440 mg, 94%). MS (ES+) *m/z*: 233 $(M+H)^+$.

The compounds of Preparations 78-93 may be prepared essentially as described in Preparation 77 by using 4-(*tert*-butoxycabonylamino-methyl)-benzoic acid and the appropriate amine. Overall yields and MS (ES) data are shown in the Table below.



Preparation	NH-R	Compound	Yield (%)	MS (ES) *m/z*

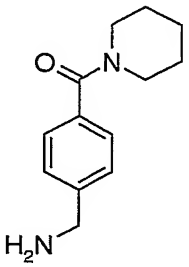
78		4-Aminomethyl-*N*-(2,2,3,3,3-pentafluoro-propyl)-benzamide	100	283 $(M+H)^+$
79		(±)-4-Aminomethyl-*N*-(2,2,2-trifluoro-1-methyl-ethyl)-benzamide	78	247 $(M+H)^+$
80		4-Aminomethyl-*N*-(3,3,3-trifluoro-propyl)-benzamide	100	247 $(M+H)^+$
81		(±)-4-Aminomethyl-*N*-(3,3,3-trifluoro-1-methyl-propyl)-benzamide	100	261 $(M+H)^+$
82		4-Aminomethyl-*N*-(cyclopentyl)-benzamide	100	219 $(M+H)^+$
Preparation	**NH-R**	**Compound**	**Yield (%)**	**MS (ES) *m/z***
83		4-Aminomethyl-*N*-(cyclohexyl)-benzamide	100	233 $(M+H)^+$
84		4-Aminomethyl-*N*-(cycloheptyl)-benzamide	80	247 $(M+H)^+$
85		4-Aminomethyl-*N*-(tetrahydro-pyran-4-yl)-benzamide	56	ND
86		4-Aminomethyl-*N*-(4-methyl-phenyl)-benzamide	100	239 $(M-H)^-$
87		4-Aminomethyl-*N*-(4-chloro-phenyl)-benzamide	84	259 $(M-H)^-$
88		4-Aminomethyl-*N*-benzyl-benzamide	59	241 $(M+H)^+$
89		4-Aminomethyl-*N*-(3,4-difluoro-phenyl)-benzamide	100	ND
90		(*R*)-4-Aminomethyl-*N*-(1-phenyl-ethyl)-benzamide	94	255 $(M+H)^+$
91		(*S*)-4-Aminomethyl-*N*-(1-phenyl-ethyl)-benzamide	94	255 $(M+H)^+$
92		4-Aminomethyl-*N*-(1-methyl-1-phenyl-ethyl)-benzamide	22	269 $(M+H)^+$

93		(±)-4-Aminomethyl-*N*-(1-methyl-2-phenyl-ethyl)-benzamide	85	269 $(M+H)^+$

ND = Not determined

Preparation 94

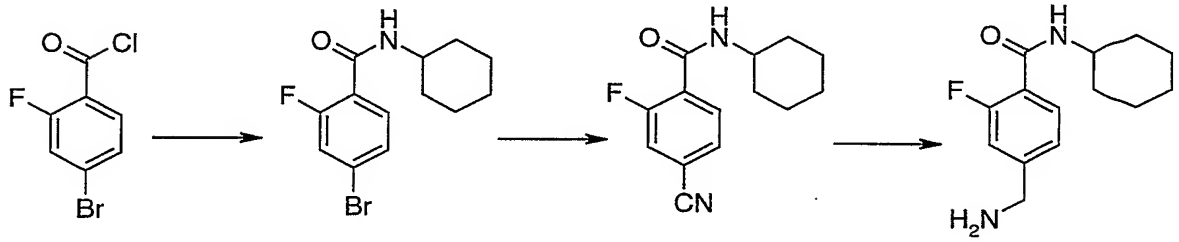
4-(Piperidin-1-ylcarbonyl)-benzylamine



Use the General Procedure 6-1, using piperidine (373 mg, 4.4 mmol) and 4-(*tert*-butoxycabonylamino-methyl)-benzoic acid to give the title compound as a white solid (1.03 g, 100%). MS (ES+) *m/z*: 219 $(M+H)^+$.

Preparation 95

4-Aminomethyl-*N*-cyclohexyl-2-fluoro-benzamide



4-Bromo-*N*-cyclohexyl-2-fluoro-benzamide: Dissolve 4-bromo-2-fluoro-benzoyl chloride (1 g, 4.21 mmol) in DCM and cool the solution in an ice bath. Add triethylamine (0.87 mL, 6.32 mmol) and cyclohexylamine (502 mg, 5.1 mmol) and stir the mixture at ambient temperature for 2 h. Partition the reaction mixture between brine and DCM. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo* to give the desired intermediate as a white solid (1.24 g, 98%).

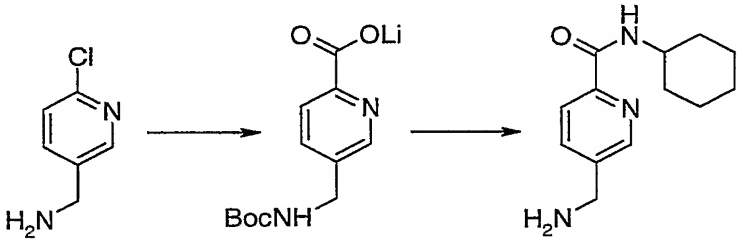
4-Cyano-*N*-cyclohexyl-2-fluoro-benzamide: Heat a mixture of 4-bromo-*N*-cyclohexyl-2-fluoro-benzamide (1.24 g, 4.13 mmol) and copper cyanide (740 mg, 8.26 mmol) in

DMF (20 mL) to reflux for 16 h. Cool the mixture to ambient temperature, add aqueous ethylenediamine and stir for 30 min. Extract the mixture with hexane/EtOAc (1:1), dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (5:1) to give the desired intermediate as a white solid (620 mg, 61%). MS (ES-) *m/z*: 245 $(M-H)^-$.

4-Aminomethyl-*N*-cyclohexyl-2-fluoro-benzamide: Dissolve 4-cyano-*N*-cyclohexyl-2-fluoro-benzamide (620 mg, 2.5 mmol) in 7N ammonia in methanol (150 mL) and hydrogenate at 500 psi pressure in the presence of Raney® nickel (500 mg) for 16 h at 60°C. Filter the mixture and concentrate *in vacuo*. Purify by SCX chromatography to give the title compound as a white solid (600 mg, 94%). MS (ES-) *m/z*: 251 $(M-H)^-$.

Preparation 96

5-(Aminomethyl)-pyridine-2-carboxylic acid cyclohexylamide



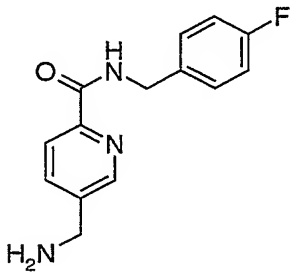
Lithium 5-(*tert*-butoxycarbonylamino-methyl)-pyridine-2-carboxylate: Dissolve 5-aminomethyl-2-chloro-pyridine (2 g, 14 mmol) and di-*tert*-butyl-dicarbonate (3.37 g, 15.4 mmol) in DCM (30 mL) and stir at room temperature for 2 h. Concentrate the reaction mixture and purify by chromatography on silica gel eluting with hexane/EtOAc (10:1 and 5:1) to give 5-(*tert*-butoxycarbonylamino-methyl)-2-chloro-pyridine as a yellow solid (3.6 g, 100%). MS (ES+) *m/z*: 243 $(M+H)^+$. Dissolve 5-(*tert*-butoxycarbonylamino-methyl)-2-chloro-pyridine (1 g, 4.12 mmol) in a mixture of ethanol (15 mL) and DMF (5 mL), and add potassium carbonate (427 mg, 3.09 mmol), palladium(II) acetate (92 mg, 0.4 mmol) and diphenylphosphinoferrocene (240 mg, 0.44 mmol). Pressurize the mixture to 15 psi with carbon monoxide gas and heat the reaction mixture to 90°C for 16 h. Filter the reaction mixture, concentrate the filtrate, and partition the residue between water and hexane/EtOAc (1:1). Dry the organic layer over Na_2SO_4, filter, and concentrate *in vacuo*. Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (3:2) to

give 5-(*tert*-butoxycarbonylamino-methyl)-pyridine-2-carboxylic acid ethyl ester as a brown oil (920 mg, 80%). MS (ES+) *m/z*: 281 $(M+H)^+$. Dissolve 5-(*tert*-butoxycarbonylamino-methyl)-pyridine-2-carboxylic acid ethyl ester (920 mg, 3.28 mmol) in a mixture of water/THF (1:2, 15 mL) and add lithium hydroxide (87 mg, 3.61 mmol). Stir the mixture at ambient temperature for 4 h and concentrate to a solid. Dry the material by azeotrope distillation with toluene to give the desired intermediate as a brown solid (1 g, 100%). MS (ES+) *m/z*: 253 $(M+H)^+$.

5-(Aminomethyl)-pyridine-2-carboxylic acid cyclohexylamide: Use the General Procedure 6-2, using cyclohexylamine (1 mL), lithium 5-(*tert*-butoxycarbonylamino-methyl)-pyridine-2-carboxylate (1 g, 3.96 mmol) and DIEA (5 mL) as cosolvent, to give the title compound as a white solid (200 mg, 22%). MS (ES+) *m/z*: 234 $(M+H)^+$.

Preparation 97

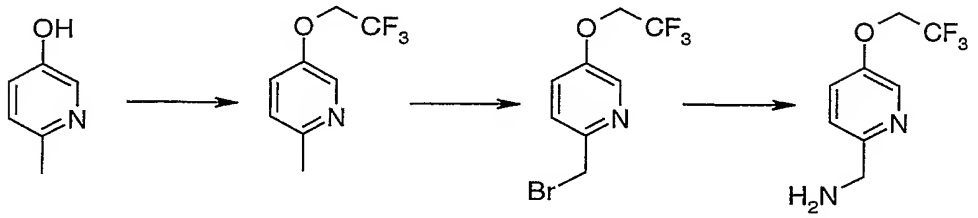
5-(Aminomethyl)-pyridine-2-carboxylic acid 4-fluoro-benzylamide



Use the General Procedure 6-2, using 4-fluoro-benzylamine (551 mg, 4.4 mmol), lithium 5-(*tert*-butoxycarbonylamino-methyl)-pyridine-2-carboxylate (740 mg, 2.93 mmol) and DIEA (2.6 mL) as cosolvent, to give the title compound as a white solid (200 mg, 26%). MS (ES+) *m/z*: 260 $(M+H)^+$.

Preparation 98

2-Aminomethyl-5-(2,2,2-trifluoroethoxy)-pyridine



2-Methyl-5-(2,2,2-trifluoroethoxy)-pyridine: Add 5-hydroxy-2-methyl-pyridine (3.3 g, 30.6 mmol), potassium carbonate (17 g, 122.4 mmol) and 2-bromo-1,1,1-trifluoroethane (10 g, 61.2 mmol) to a flask containing DMF (60 mL) and heat to 95°C for 20 h. Cool the mixture, dilute with aqueous 10% NaCl (20 mL) and extract with hexane/EtOAc (1:1, 100 mL). Filter the bi-phasic mixture through Celite®, separate and wash the organic layer with aqueous 10% NaCl (3 x 50 mL) and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 1:1) to obtain the desired intermediate (4.1 g, 70%).

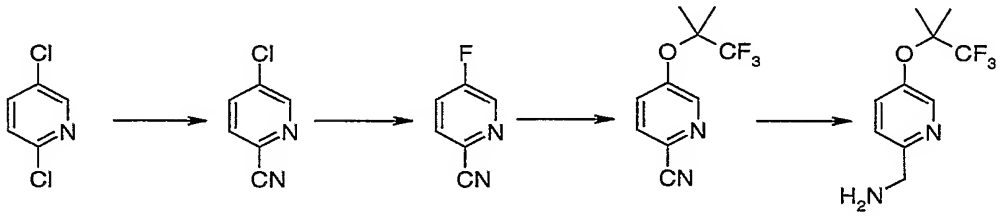
2-Bromomethyl-5-(2,2,2-trifluoroethoxy)-pyridine: Add 2-methyl-5-(2,2,2-trifluoroethoxy)-pyridine (2.5 g, 13.1 mmol), NBS (2.3 g, 13.1 mmol) and benzoyl peroxide (50 mg) to a flask containing carbon tetrachloride (30 mL). Heat the mixture at 80°C in a sealed flask for 16 h. Cool the flask, add NBS (1.1 g, 6.5 mmol) and benzoyl peroxide (100 mg), then continue heating at 80°C for an additional 5 h. Cool the mixture, dilute with DCM, then wash with saturated sodium bisulfite (10 mL). Collect the organic layer and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to obtain the desired intermediate (460 mg, 13%).

2-Aminomethyl-5-(2,2,2-trifluoroethoxy)-pyridine: Dissolve sodium azide (270 mg, 4.0 mmol) in DMF (30 mL). Cool the solution to 0°C, then add 2-bromomethyl-5-(2,2,2-trifluoroethoxy)-pyridine (440 mg, 1.6 mmol) at 0°C. Slowly heat the mixture from 0°C to 80°C over 30 min. Cool the reaction, dilute with EtOAc (100 mL) and wash with 10% aqueous NaCl (3 x 25 mL). Collect the organic layer and concentrate *in vacuo* to a volume of 50 mL. Transfer the solution to a pressure vessel. Add 10 % Pd/C (Degussa

type E101, 50% water by wt, 500 mg) and pressurize the vessel under hydrogen (10 psi) for 1 h with stirring. Filter the mixture through Celite® and wash filter cake with warm methanol followed by DCM. Concentrate *in vacuo*, then purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (20:1) to obtain the title compound (180 mg, 54%). MS (ES+) *m/z*: 207 $(M+H)^+$.

Preparation 99

2-Aminomethyl-5-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-pyridine



5-Chloro-pyridine-2-carbonitrile: Add 2,5-dichloropyridine (6.0 g, 40.5 mmol), zinc cyanide (2.9 g, 24.7 mmol), zinc dust (116 mg, 1.8 mmol) and 1,1'-[bis(diphenylphosphino)ferrocene]dichloropalladium(II) (20 mg, 0.98 mmol) to a flask containing DMF (40 mL). Heat the mixture to reflux for 5 h, then cool to ambient temperature. Dilute the mixture with EtOAc (300 mL) and wash with 10% aqueous NaCl (3x75 mL). Collect the organic layer, concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 1:1) to obtain the desired intermediate (2.6 g, 46%).

5-Fluoro-pyridine-2-carbonitrile: Add 5-chloro-pyridine-2-carbonitrile (3.0 g, 21.7 mmol) and potassium fluoride (3.9 g, 67.1 mmol) to a flask containing NMP (75 mL). Heat the mixture to reflux for 16 h. Add additional potassium fluoride (1.0 g, 17.2 mmol) and NMP (10 mL), then continue heating at reflux for 3 h. Cool the mixture, dilute with EtOAc, then wash with saturated NaCl (3 x 50 mL). Collect the organic layer, concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (20:1) to obtain the desired intermediate (1.5 g, 53%).

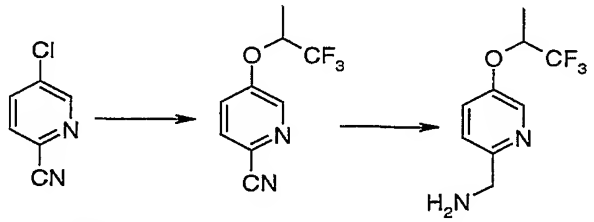
5-(2,2,2-Trifluoro-1,1-dimethyl-ethoxy)-pyridine-2-carbonitrile: Add 2-trifluoromethyl-2-propanol (1.1 g, 8.3 mmol) slowly to a slurry of sodium hydride (202

mg, 60% mineral oil, washed with hexane) in HMPA (3 mL) under nitrogen. Stir the slurry for 15 min, then add 5-fluoro-pyridine-2-carbonitrile (510 mg, 4.2 mmol). Stir the slurry for 16 h at ambient temperature. Adjust the mixture to pH 9 with sodium carbonate then extract with diethyl ether (3 x 50 mL). Collect the organic layer, dry over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (95/5 to 80/20) to obtain the desired intermediate (768 mg, 79%). GC-MS *m/z*: 230 (M^+).

2-Aminomethyl-5-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-pyridine: Add 5-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-pyridine-2-carbonitrile (580 mg, 2.5 mmol), 10 % Pd/C (Degussa type E101, 50% water by wt, 400 mg) and trifluoroacetic acid (2 mL) in ethanol (20 mL) to a pressure vessel. Pressurize the vessel to 50 psi with hydrogen for 1 h. Filter the mixture through Celite® and wash the cake with warm ethanol followed by DCM under a nitrogen atmosphere. Concentrate *in vacuo* to obtain the crude product as the trifluoroacetic acid salt. Prepare the free base with SCX chromatography, then purify using silica gel chromatography eluting with DCM/2M ammonia in methanol (20:1) to obtain the title compound (261 mg, 45%). MS (ES+) *m/z*: 235 $(M+H)^+$.

Preparation 100

(±)-2-Aminomethyl-5-(2,2,2-trifluoro-1-methyl-ethoxy)-pyridine



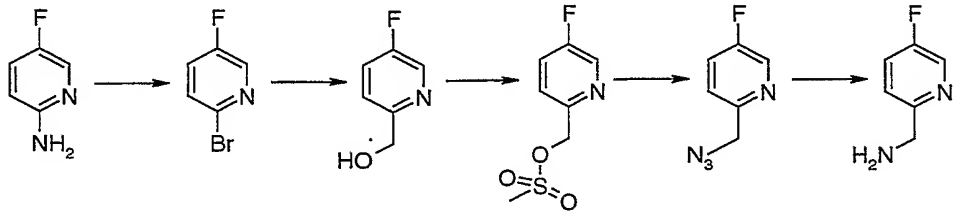
(±)-5-(2,2,2-Trifluoro-1-methyl-ethoxy)-pyridine-2-carbonitrile: Add 1,1,1-trifluoro-2-propanol (971 mg, 8.5 mmol) slowly to a slurry of sodium hydride (205 mg, 60% mineral oil, washed with hexane) in HMPA (8 mL) under nitrogen at 0°C. Allow the slurry to warm to ambient temperature and stir for 5 min. Add 5-chloro-pyridine-2-carbonitrile (590 mg, 4.2 mmol), then heat the mixture at 90°C for 4 h. Adjust the mixture to pH 9 with sodium carbonate then extract with diethyl ether (2 x 50 mL). Dry the combined organic extracts over Na_2SO_4 and concentrate *in vacuo*. Purify by

chromatography on silica gel eluting with hexane/EtOAc (95/5 to 80/20) to obtain the desired intermediate (818 mg, 89%). GC-MS *m/z*: 216(M^+).

(±)-2-Aminomethyl-5-(2,2,2-trifluoro-1-methyl-ethoxy)-pyridine: Add (±)-5-(2,2,2-trifluoro-1-methyl-ethoxy)-pyridine-2-carbonitrile (810 mg, 3.7 mmol), 10 % Pd/C (Degussa type E101, 50% water by wt, 300 mg), and trifluoroacetic acid (4 mL) in methanol (50 mL) to a pressure vessel. Pressurize the vessel to 40 psi with hydrogen for 0.25 h. Filter the mixture through Celite® and wash the cake with warm ethanol followed by DCM under a nitrogen atmosphere. Concentrate *in vacuo* to obtain the crude product as a trifluoroacetic acid salt. Prepare the free base with SCX ion chromatography, then purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (20:1) to obtain the title compound (676 mg, 82%). GC-MS *m/z*: 220 (M^+).

Preparation 101

2-Aminomethyl-5-fluoro-pyridine



2-Bromo-5-fluoro-pyridine: Cool 48% hydrobromic acid (44 mL, 4.4 equiv.) in an ice/acetone bath to –5°C, then add 2-amino-5-fluoropyridine (10.0 g, 89.2 mmol, 1.0 equiv.) portion wise over 10 min and maintain the temperature below 5°C throughout addition. Add bromine (14 mL, 3 equiv.) at 0°C over 2 h and maintain the temperature at 0°C throughout the addition. Stir the mixture for 30 min, then add a solution of sodium nitrite (15.4 g) in water (30 mL) via addition funnel over 2 h and maintain the temperature below 0°C throughout the addition. Stir the mixture for 30 min., then add a solution of NaOH (34 g) in water (34 mL) over 1 h and maintain the temperature below 10°C. Stir the mixture for 3 min. Extract with diethyl ether (5 x 250 mL), dry the combined organic extracts over Na_2SO_4 and concentrate *in vacuo* to give the desired intermediate (12.1 g, 77%).

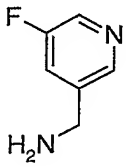
(5-Fluoro-pyridin-2-yl)-methanol: At –78°C under nitrogen, add *n*-butyllithium (2.5 M in hexane, 16.4 mL, 40.9 mmol) via syringe to a solution of 2-bromo-5-fluoro-pyridine (6.0 g, 34.1 mmol) in toluene (220 mL), while keeping the reaction temperature below –60°C. Stir the mixture at –78°C and then add DMF (3.4 mL, 44.3 mmol) and stir for 1 h at this temperature. Warm to –10°C and quench with methanol (10 mL). Concentrate the mixture to half of the volume *in vacuo*. Dilute with methanol (150 mL), cool the mixture to –78°C and add sodium borohydride (3.2 g, 85.2 mmol) portion wise over 5 min. Warm the mixture to ambient temperature and stir for 2 h. Quench with water (10 mL) and remove the organic solvent *in vacuo* to obtain an oil/water mixture. Extract with diethyl ether (3 x 100 mL), dry the combined organic extracts, wash with brine, dry and concentrate *in vacuo* to obtain the desired intermediate as an oil (3.9 g, 91%).

Methanesulfonic acid (5-fluoro-pyridin-2-yl)methyl ester: Add methanesulfonyl chloride (1.8 mL, 23.5 mmol) to a solution of (5-fluoro-pyridin-2-yl)-methanol (2.5 g, 19.7 mmol) and triethylamine (8.2 mL, 59.0 mmol) in DCM (150 mL) at 0°C under nitrogen. Stir the mixture for 30 min and concentrate *in vacuo*. Dilute with water (20 mL) and extract the mixture with EtOAc (3 x 50 mL). Combine the organic extracts and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc to obtain the desired intermediate (2.2 g, 54%).

2-Aminomethyl-5-fluoro-pyridine: Dissolve methanesulfonic acid (5-fluoro-pyridin-2-yl)-methyl ester (1.5 g, 7.3 mmol) in DMF (5mL) and add sodium azide (950 mg, 14.6 mmol). Stir the mixture for 30 min, then dilute with hexane/EtOAc (1:1, 50 mL). Wash the mixture with 10% aqueous NaCl (3 x 10 mL). Dry the combined organic extracts over Na_2SO_4 and remove half of the solvent *in vacuo*. Add EtOAc (20 mL) and a suspension of 10% Pd/C (200 mg) in EtOAc (2 mL). Stir the mixture for 1 h at ambient temperature in a pressurized vessel under 50 psi of hydrogen. Filter the slurry through Celite® and concentrate *in vacuo* to obtain 2-aminomethyl-5-fluoro-pyridine (613 mg, 60% yield, 80% purity by GC/MS). GC-MS *m/z*: 126 (M^+).

Preparation 102

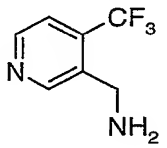
3-Aminomethyl-5-fluoro-pyridine



In a Parr Bottle add 2,6-dichloro-3-cyano-5-fluoropyridine (20 g, 0.105 mol), ethanol (336 mL), triethylamine (24 mL), and 5% Pd/C (4 g). Place on a Parr Shaker Apparatus under 60 psi hydrogen for 1 h at ambient temperature. Filter the reaction mixture and bubble ammonia gas into filtrate for 10 min. Add Raney® nickel (5.2 g) and place on a Parr Shaker Apparatus under 500 psi hydrogen for 18 h at 60-70°C. Filter the reaction mixture and concentrate *in vacuo*. Dissolve in methanol and add 1N hydrogen chloride in ether until form a precipitate. Cool in an ice bath, filter off the precipitate, wash the solid several times with ether, and dry to give the title compound as the hydrochloride salt (12 g, 70%). MS (ES+) *m/z*: 127 $(M+H)^+$. Dissolve the hydrochloride salt in water, add 0.1 N aqueous NaOH to adjust to pH 10, extract with DCM, dry the organic layer over Na_2SO_4, filter and concentrate to give the title compound.

Preparation 103

3-Aminomethyl-4-trifluoromethyl-pyridine

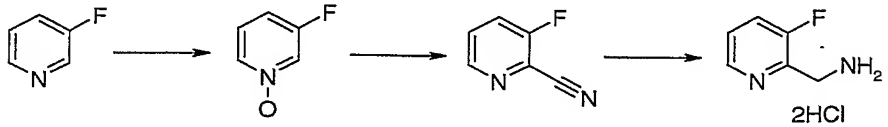


Add 4-trifluoromethyl-nicotinonitrile (1.0 g, 5.8 mmol) and ethanol wet Raney® activated nickel (0.2 g) to a Parr pressure vessel. Immediately add, at ambient temperature, 2B-ethanol (25 mL) previously saturated with ammonia gas and seal the vessel. Purge the reaction vessel with nitrogen, pressurize the reaction mixture with hydrogen (400 KPa), seal the vessel, agitate the reaction and heat to 40°C. Continue the reaction for 20 h then turn off the heat and allow the reaction mixture to cool to ambient temperature. Vent the excess hydrogen from the vessel and purge the vessel with nitrogen. Filter the reaction mixture to remove the Raney® nickel, wash with ethanol and

concentrate in *vacuo*. Purify by SCX chromatography to give the title compound (560 mg, 55%). MS (ES+) *m/z*: 177 $(M+H)^+$.

Preparation 104

2-Aminomethyl-6-fluoropyridine Dihydrochloride



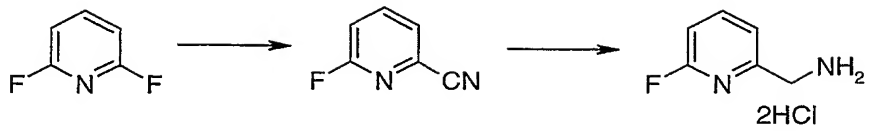
3-Fluoropyridine-*N*-Oxide: Dissolve 3-fluoropyridine (2.5 g, 25.749 mmol) in anhydrous DCM (75 mL). Add *m*-CPBA (70% suspension, 12.696 g, 51.499 mmol) and stir at ambient temperature overnight. Wash the reaction mixture with saturated aqueous $NaHCO_3$, dry the organic phase over Na_2SO_4, filter, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with DCM and DCM/methanol (97:3) to obtain the desired intermediate as a solid (1.413 g, 49%). MS (ES+) *m/z*: 115 $(M+H)^+$.

2-Cyano-3-fluoropyridine: **Dissolve 3-fluoropyridine-*N*-oxide (1.0 g, 8.687 mmol) in** anhydrous acetonitrile (100 mL). Add triethylamine (1.319 g, 1.82 mL, 13.031 mmol), trimethylsilylcyanide (3.447 g, 4.63 mL, 34.749 mmol) and heat the mixture to reflux overnight. Cool to ambient temperature and concentrate *in vacuo*. Dissolve the residue in EtOAc and wash with saturated aqueous $NaHCO_3$. Dry the organic layer over Na_2SO_4, filter, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 17:3) to give the desired intermediate as a solid (746 mg, 70%). GC-MS *m/z*: 122 (M^+).

2-Aminomethyl-3-fluoropyridine dihydrochloride: Dissolve 2-cyano-3-fluoropyridine (300 mg, 2.457 mmol) in absolute ethanol (12 mL). Add 10% Pd/C (93 mg) and concentrated HCl (0.614 mL, 7.37 mmol). Hydrogenate at 40 psi overnight. Filter through Celite® and concentrate *in vacuo* to give the title compound as a solid (440 mg, 90%). MS (ES+) *m/z*: 127 $(M+H)^+$.

Preparation 105

2-Aminomethyl-6-fluoropyridine Dihydrochloride

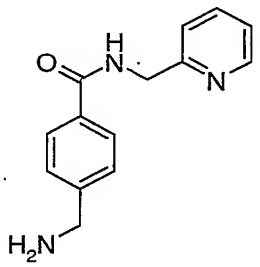


2-Cyano-6-fluoropyridine: Dissolve 2,6-difluoropyridine (12 g, 104.2 mmol) in anhydrous DMSO (5 mL). Add a solution of sodium cyanide (1.3 g, 26.53 mmol) in DMSO (60 mL) over 12 h using a syringe pump. Heat the mixture to 100°C overnight. Cool to ambient temperature, dilute with EtOAc (500 mL), and wash with brine. Dry the organic phase over Na_2SO_4, filter, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 4:1) to give the desired intermediate as a solid (723 mg, 22%). GC-MS *m/z*: 122 (M^+).

2-Aminomethyl-6-fluoropyridine Dihydrochloride: Dissolve 2-cyano-6-fluoropyridine (300 mg, 2.46 mmol) in absolute ethanol (12 mL). Add 10% Pd/C (93 mg) and concentrated HCl (0.614 mL, 7.37 mmol). Hydrogenate at 40 psi overnight. Filter through Celite® and concentrate to give the title compound as a solid (356 mg, 73%). MS (ES+) *m/z*: 127 $(M+H)^+$.

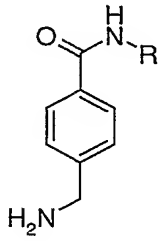
Preparation 106

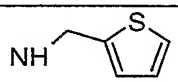
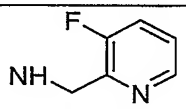
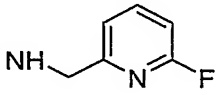
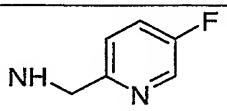
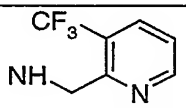
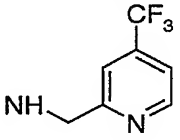
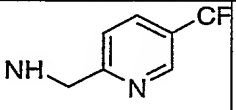
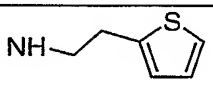
4-Aminomethyl-*N*-(pyridin-2-yl-methyl)-benzamide

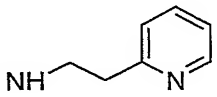
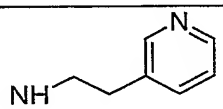
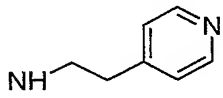


Use the General Procedure 6-2, using 2-(aminomethyl)pyridine (181 mg, 0.172 mL, 1.67 mmol) and 4-(*tert*-butoxycarbonylamino-methyl)-benzoic acid (420 mg, 1.67 mmol) to give the title compound as a solid (427 mg, 100 %). MS (ES+) *m/z*: 242 $(M+H)^+$.

The compounds of Preparations 107-117 may be prepared essentially as described in Preparation 106 by using 4-(*tert*-butoxycarbonylamino-methyl)-benzoic acid and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.

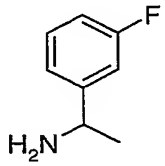


Prep.	NHR	Compound	Yield (%)	MS (ES+) or GC-MS
107		4-Aminomethyl-*N*-(thiophen-2-yl-methyl)-benzamide	100	247 $(M+H)^+$
108		4-Aminomethyl-*N*-(3-fluoro-pyridin-2-ylmethyl)-benzamide	58	259 $(M)^+$
109		4-Aminomethyl-*N*-(6-fluoro-pyridin-2-ylmethyl)-benzamide	98	259 $(M)^+$
110		4-Aminomethyl-*N*-(5-fluoro-pyridin-2-ylmethyl)-benzamide	67	259 $(M)^+$
111		4-Aminomethyl-*N*-(3-trifluoromethyl-pyridin-2-ylmethyl)-benzamide	62	310 $(M+H)^+$
112		4-Aminomethyl-*N*-(4-trifluoromethyl-pyridin-2-ylmethyl)-benzamide	76	309 $(M)^+$
113		4-Aminomethyl-*N*-(5-trifluoromethyl-pyridin-2-ylmethyl)-benzamide	65	310 $(M+H)^+$
114		4-Aminomethyl-*N*-(2-thiophen-2-yl-ethyl)-benzamide	100	261 $(M+H)^+$

Prep.	NHR	Compound	Yield (%)	MS (ES+) or GC-MS
115		4-Aminomethyl-*N*-(2-pyridin-2-yl-ethyl)-benzamide	81	256 $(M+H)^+$
116		4-Aminomethyl-*N*-(2-pyridin-3-yl-ethyl)-benzamide	97	256 $(M+H)^+$
117		4-Aminomethyl-*N*-(2-pyridin-4-yl-ethyl)-benzamide	96	256 $(M+H)^+$

Preparation 118

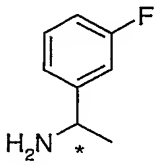
(±)-1-(3-Fluorophenyl)ethylamine



Add sodium cyanoborohydride (452 mg, 7.2 mmol) to a solution of 3-fluoroacetophenone (500 mg, 3.6 mmol) and ammonium acetate (2.8 g, 36 mmol) in methanol (11 mL). Stir the mixture for 96 h at ambient temperature under a nitrogen atmosphere. Adjust to pH 2 with 2M hydrogen chloride in diethyl ether. Concentrate the slurry *in vacuo*, dilute the residue with DCM and wash with 5N aqueous NaOH followed by saturated aqueous $NaHCO_3$. Dry the organic layer, concentrate *in vacuo* to half of the volume, and load the solution onto a SCX column (pre-wash column with methanol followed by DCM, then elute with 2M ammonia in methanol). Concentrate the fractions to half of the volume to remove ammonia, add excess of 2M hydrogen chloride in diethyl ether and concentrate to obtain the hydrochloride salt (70:30 mixture of title compound and dimer). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (20:1) to obtain the title compound (323 mg, 51%). MS (ES+) *m/z*: 140 $(M+H)^+$

Preparation 119

1-(3-Fluorophenyl)ethylamine, Isomer 2



Set-up flask equipped with condenser, mechanical stirrer and addition funnel. Add 3-fluoroacetophenone (25 g, 0.18 mol) and formic acid (4.2 g, 0.09 mol) via addition funnel to a flask containing formamide (32.6 g, 0.72 mol) at 140°C over 15 min, and then heat the mixture to 160°C. Add formic acid successively (4.2 g, 0.5 equiv.) via addition funnel to the flask every hour for 4 h while maintaining the reaction temperature at 160°C. Cool the reaction mixture, extract with toluene (3 x 100 mL), and concentrate the organic layer *in vacuo*. Add aqueous HCl (37%, 40 mL) to the residue and heat to reflux for 2 h. Cool to ambient temperature and wash the aqueous mixture with toluene (2 x 100 mL), then basify the aqueous mixture with 5N aqueous NaOH (120 mL). Extract the basic mixture with EtOAc (3 x 100 mL), dry the combined organic extracts over Na_2SO_4 and filter. Acidify the filtrate with 2M hydrogen chloride in diethyl ether to pH 2 and concentrate *in vacuo* to a solid. Suspend the solid in diethyl ether, filter and wash with diethyl ether. Dry the solid in a vacuo-oven at 50°C to obtain (±)-1-(3-fluorophenyl)ethylamine hydrochloride (21.5 g, 68%). MS (ES+) *m/z*: 140 $(M+H)^+$.

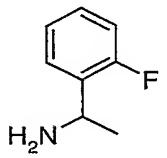
Dissolve (±)-1-(3-fluorophenyl)ethylamine hydrochloride (42.5 g, 0.24 mol) in THF (520 mL) and saturated aqueous $NaHCO_3$ (430 mL). Add di-*tert*-butyl-dicarbonate (69 g, 0.31 mol) and stir for 16 h at ambient temperature. Separate the organic layer, dilute with EtOAc (300 mL) and wash with 2N aqueous NaOH (1 x 400 mL) and water (2 x 200 mL). Concentrate the organic layer *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to obtain (±)-*N*-[1-(3-fluorophenyl)ethyl]-carbamic acid *tert*-butyl ester (56 g, 97%). GC-MS *m/z*: 183 $[(M-C_4H_9)^+]$.

Separate the racemic mixture of (±)-*N*-[1-(3-fluorophenyl)ethyl]-carbamic acid *tert*-butyl ester by normal phase chiral chromatography (Chiralcel OD 8 x 34 cm, elute with 95:5, heptane/isopropanol). Using the General Procedure 1-4, deprotect the desired

isomer [20.7 g, >95% ee (Chiralcel OD, 4.6 x 250 mm, eluent: 95:5 heptane/isopropanol with 0.2% DMEA, 1.0 mL/min)] to obtain the title compound (9.4 g, 78%). MS (ES+) *m/z*: 140 $(M+H)^+$.

Preparation 120

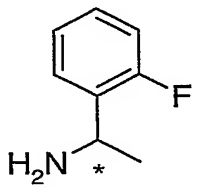
(±)-1-(2-Fluorophenyl)ethylamine



Add sodium cyanoborohydride (1.8 g, 29 mmol) to a solution of 2-fluoro-acetophenone (2.0 g, 14.5 mmol) and ammonium acetate (11.2 g, 145 mmol) in methanol (45 mL). Stir the mixture for 20 h at ambient temperature under a nitrogen atmosphere. Adjust the mixture to pH 1 with 2M hydrogen chloride in diethyl ether. Concentrate the slurry *in vacuo*, dilute the residue with DCM and wash with 5N aqueous NaOH. Dry the organic layer, concentrate carefully, as the amine is volatile, under reduced pressure to one third of the volume, and load the material onto an SCX column (pre-wash column with methanol, followed by DCM, elute with 2M ammonia in methanol). Concentrate the fraction to one half of the volume to remove the ammonia, then add excess 2M hydrogen chloride in diethyl ether and concentrate to obtain the hydrochloride salt. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (20:1) to obtain the title compound (280 mg, 13%). MS (ES+) *m/z*: 140 $(M+H)^+$.

Preparation 121

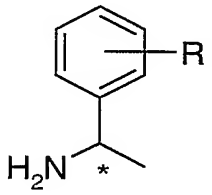
1-(2-Fluorophenyl)ethylamine, Isomer 1



Use a method similar to the General Procedure 6-3, using 2-fluoroacetophenone (1.4 g, 9.9 mmol) and (*R*)-(+)-2-methyl-2-propanesulfinamide (1.0 g, 8.2 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc/2M ammonia in methanol

(90:9:1 to 50:45:5). Add 4M hydrogen chloride in dioxane to obtain the title compound as the hydrochloride (600 mg, 35%). MS (ES+) *m/z*: 140 $(M+H)^+$. Dissolve the hydrochloride in an aqueous solution of cesium carbonate (1.5 equiv.) and extract with toluene to obtain the free base.

The compounds of Preparations 122-141 may be prepared essentially as described in Preparation 121 by using (*R*)-(+)-2-methyl-2-propanesulfinamide or (*S*)-(-)-2-methyl-2-propanesulfinamide and the appropriate acetophenone. Overall yields and mass spectrum data are shown in the Table below.



Prep.	R	Compound	Yield (%)	MS (ES+) or GC-MS
122	3-CN	1-(3-Cyanophenyl)ethylamine, Isomer 1	37	130 $(M+H-NH_3)^+$
123	3-CN	1-(3-Cyanophenyl)ethylamine, Isomer 2	49	130 $(M+H-NH_3)^+$
124	4-CN	1-(4-Cyanophenyl)ethylamine, Isomer 1	49	130 $(M+H-NH_3)^+$
125	4-CN	1-(4-Cyanophenyl)ethylamine, Isomer 2	49	130 $(M+H-NH_3)^+$
126	2-Cl	1-(2-Chlorophenyl)ethylamine, Isomer 1	25	156 $(M+H)^+$
127	3-Cl	1-(3-Chlorophenyl)ethylamine, Isomer 1	68	156 $(M+H)^+$
128	3-CF_3	1-(3-Trifluoromethylphenyl)-ethylamine, Isomer 1	40	190 $(M+H)^+$
129	4-CF_3	1-(4-Trifluoromethylphenyl)-ethylamine, Isomer 2	70	190 $(M+H)^+$

Prep.	R	Compound	Yield (%)	MS (ES+) or GC-MS
130	3-Cl,4-F	1-(3-Chloro-4-fluorophenyl)-ethylamine, Isomer 1	66	174 $(M+H)^+$
131	3-Cl-4-F	1-(3-Chloro-4-fluorophenyl)-ethylamine, Isomer 2	68	174 $(M+H)^+$
132	2,3-diF	1-(2,3-Difluorophenyl)-ethylamine, Isomer 1	20	141 $(M+H-NH_3)^+$
133	2,3-diF	1-(2,3-Difluorophenyl)-ethylamine, Isomer 2	45	141 $(M+H-NH_3)^+$
134	2,4-diF	1-(2,4-Difluorophenyl)-ethylamine, Isomer 1	58	158 $(M+H)^+$
135	2,4-diF	1-(2,4-Difluorophenyl)-ethylamine, Isomer 2	49	158 $(M+H)^+$
136	3,5-diF	1-(3,5-Difluorophenyl)-ethylamine, Isomer 1	26	158 $(M+H)^+$
137	3,5-diF	1-(3,5-Difluorophenyl)-ethylamine, Isomer 2	83	158 $(M+H)^+$
138	3,4-diF	1-(3,4-Difluorophenyl)-ethylamine, Isomer 1	67	158 $(M+H)^+$
139	3,4-diF	1-(3,4-Difluorophenyl)-ethylamine, Isomer 2	77	158 $(M+H)^+$
140	3,4,5-triF	1-(3,4,5-Trifluorophenyl)-ethylamine, Isomer 2	20	176 $(M+H)^+$
141	3,5-diCF_3	1-(3,5-bis-trifluoromethylphenyl)-ethylamine, Isomer 2	49	258 $(M+H)^+$
142	2-OCF_3	1-(2-Trifluoromethoxyphenyl)-ethylamine, Isomer 2	47	ND
143	2-Me	1-(2-Methyl)-ethylamine, Isomer 1	13	136 (M^+)

ND = Not determined

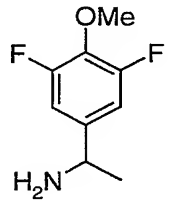
Preparation 144

(±)-1-(2,5-Difluorophenyl)ethylamine

Slurry 2',5'-difluoroacetophenone (0.9 g, 5.76 mmol), ammonium acetate (4.44 g, 57.5 mmol) and sodium cyanoborohydride (755 mg, 12 mmol) in anhydrous methanol (25 mL) and stir for 18 h at ambient temperature. Acidify with 5N aqueous HCl (5 mL), dilute, extract with ethyl ether (3 x 150 mL), basify aqueous layer with 5N aqueous NaOH, extract with DCM (3 x 75 mL), wash the organic layer with brine, dry over $MgSO_4$, filter and concentrate *in vacuo*. Purify by SCX chromatography to give a mixture of (±)-1-(2,5-difluorophenyl)ethylamine and bis-[1-(±)-2,5-difluorophenyl)ethyl]-amine (total 400 mg, crude weight). MS (ES+) *m/z*: 158 $(M+H)^+$ and *m/z*: 298 $(M+H)^+$.

Preparation 145

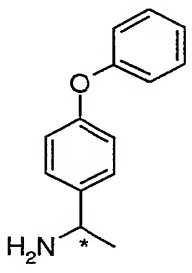
(±)-1-(3,5-Difluoro-4-methoxyphenyl)ethylamine



Slurry 3',5'-difluoro-4'-methoxyacetophenone (1.0 g, 5.0 mmol), ammonium acetate (4.14 g, 50 mmol) and sodium cyanoborohydride (630 mg, 20 mmol) in anhydrous methanol (35 mL) and stir for 18 h at ambient temperature. Acidify with 1N aqueous HCl (5 mL), dilute, extract with ethyl ether (3 x 150 mL), basify aqueous with 1N aqueous NaOH, extract with DCM (3 x 50 mL), wash the organic extracts with brine, dry over $MgSO_4$, filter and concentrate *in vacuo*. Purify by SCX chromatography to give crude the title compound as a yellow oil (380 mg).

Preparations 146 and 147

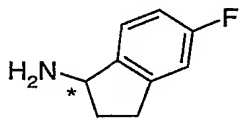
1-(4-Phenoxyphenyl)-ethylamine, Isomer 1 and Isomer 2



Mix 4-phenoxyacetophenone (5.3 g, 25 mmol), ammonium acetate (14.5 g, 187.5 mmol) and sodium cyanoborohydride (3.2 g, 50 mmol) in anhydrous methanol (200 mL). Stir for 18 h at ambient temperature. Acidify with 1N aqueous HCl (10 mL), dilute, extract with ethyl ether (3 x 150 mL), dry over $MgSO_4$, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting sequentially with hexane/EtOAc (4:1, 1:1 and 0:1) and EtOAc/methanol (1:1) to give (±)-1-(4-phenoxyphenyl)-ethylamine (1.6 g, 30%). Dissolve the racemate (1.1 g, 5.2 mmol) in DCM (100 mL), add triethylamine (1.6mL, 11.4 mmol) followed by di-*tert*-butyl-dicarbonate (1.7 g, 7.8 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give (±)-α-methyl-(4'-phenoxy)-benzylamino]carbamic acid *tert*-butyl ester as an off-white solid (1.3 mg, 81%). Separate via chiral chromatography (heptane/isopropanol/DMEA 95:5:0.2, 4.6 x 250 mm Chiralpak AD, 1 mL/min, UV detector at 260 nm) to give [α-methyl-(4'-phenoxy)benzylamino]carbamic acid *tert*-butyl ester, isomer 1 (315 mg, chiral HPLC: t_R = 7.35 min; 99.1% ee) and [α-methyl-(4'-phenoxy)benzyl-aminocarbamic acid *tert*-butyl ester, isomer 2 (400 mg, chiral HPLC: t_R = 8.7 min; 97.2% ee). Dissolve [α-methyl-(4'-phenoxy)benzylamino]carbamic acid *tert*-butyl ester isomer 1 or isomer 2 in DCM/trifluoroacetic acid (1:1, 20 mL) to give, after solvent evaporation and chromatography over SCX column, 1-(4-phenoxyphenyl)-ethylamine, isomer 1 (Preparation 146) and 1-(4-phenoxyphenyl)-ethylamine, isomer 2 (Preparation 147). MS (ES+) *m/z*: 214 $(M+H)^+$.

Preparation 148

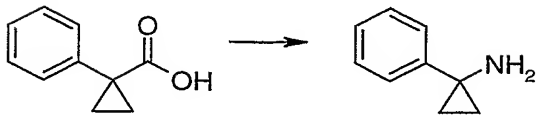
(5-Fluoro-indan-1-yl)amine, Isomer 1



Use a method similar to the General Procedure 6-3 to react 5-fluoro-indan-1-one (1.5 g, 9.9 mmol) and (*R*)-(+)-2-methyl-2-propanesulfinamide (1.0 g, 8.3 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (5:2). Add 4M hydrogen chloride in dioxane to obtain the title compound as the hydrochloride (254 mg, 16%). MS (ES+) *m/z*: 152 $(M+H)^+$. Dissolve the hydrochloride in an aqueous solution of cesium carbonate (1.5 equiv.) and extract with toluene to obtain the free base.

Preparation 149

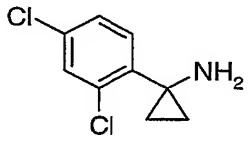
1-Phenyl-cyclopropylamine



Dissolve 1-phenyl-cyclopropanecarboxylic acid (2.5 g, 15.4 mmol) in a mixture of sulfuric acid (12.5 mL) and DCM (25 mL). Add sodium azide (2.3 g, 35.4 mmol) by small portions at ambient temperature. Heat the reaction mixture at 50°C for 8 h, cool to 0°C and slowly add 2M aqueous NaOH until pH 11. Extract the reaction mixture with DCM (3 x 100 mL), combine the organic extracts and dry over anhydrous Na_2SO_4. Evaporate the solvent and purify by chromatography on silica gel eluting with DCM and DCM/2M ammonia in methanol (9:1) to obtain the title compound as a brown oil (1.1 g, 54%). MS (ES+) *m/z*: 134 $(M+H)^+$.

Preparation 150

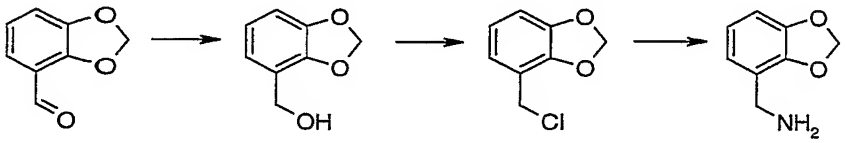
1-(2,4-Dichlorophenyl)-cyclopropylamine



Use a method similar to Preparation 149, using 1-(2,4-dichlorophenyl)-cyclopropanecarboxylic acid (3.5 g, 15.4 mmol), to obtain the title compound as a yellow oil (1.0 g, 32%). MS (ES+) *m/z*: 203 $(M+H)^+$.

Preparation 151

4-Methylamino-benzo[1,3]dioxole



Benzo[1,3]dioxol-4-yl-methanol: Dissolve benzo[1,3]dioxole-4-carbaldehyde (2.0 g, 13.3 mmol) in anhydrous THF (30 mL) and treat with sodium borohydride (0.5 g, 13.3

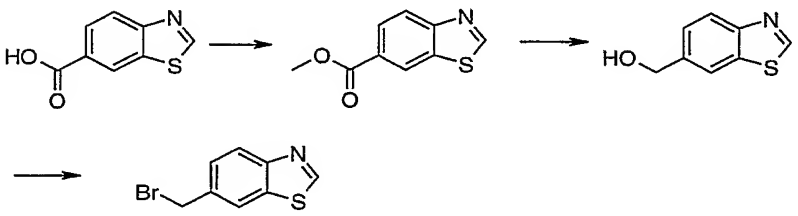
mmol) at 0°C. Stir the reaction mixture for 30 min at ambient temperature and quench with water (30 mL). Extract the reaction mixture with DCM (3 x 10 mL), combine the organic extracts and dry over anhydrous Na_2SO_4. Remove the solvent to obtain the desired intermediate as a colorless oil (1.9 g, 94%).

4-Chloromethyl-benzo[1,3]dioxole: Dissolve benzo[1,3]dioxol-4-yl-methanol (1.9 g, 12.5 mmol) in thionyl chloride (3 mL, 41.1 mmol) and reflux the reaction mixture for 1 h. Concentrate *in vacuo* to obtain the desired intermediate as a yellow oil (1.9 g, 91%) that was used without further purification. GC-MS *m/z*: 170 (M^+).

4-Methylamino-benzo[1,3]dioxole: Dissolve 4-chloromethyl-benzo[1,3]dioxole (1.9 g, 11.1 mmol) in methanol (5 mL), cool the solution to 0°C and saturate with anhydrous ammonia for 15 min. Keep the reaction mixture at 0°C for 18 h. Evaporate the solvent and purify by SCX chromatography to obtain the title compound as a yellow oil (0.6 g, 36%). GC-MS *m/z*: 151 (M^+).

Preparation 152

6-Bromomethyl-benzothiazole



Benzothiazole-6-carboxylic acid methyl ester: Add 1-methyl-3-nitro-1-nitrosoguanidine (5.0 g, 33.9 mmol) to a mixture of diethyl ether (20 mL) and 1N aqueous NaOH (20 mL) at ambient temperature. Separate the organic layer and add it slowly to a solution of benzothiazole-6-carboxylic acid (1.0 g, 5.58 mmol) in THF (50 mL) at 0°C. Evaporate the solvent to obtain the desired intermediate as a yellow solid (1.1 g, 100%). MS (ES+) *m/z*: 194 $(M+H)^+$.

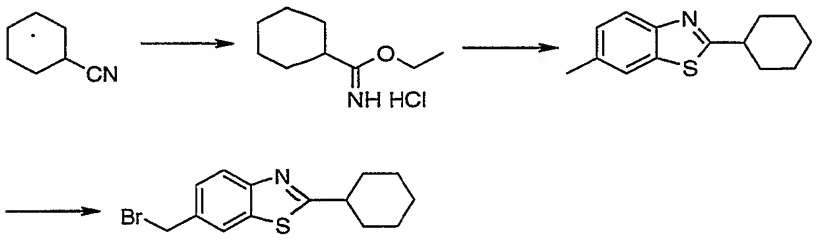
Benzothiazol-6-yl-methanol: Add slowly a solution of benzothiazole-6-carboxylic acid methyl ester (0.5 g, 2.59 mmol) in anhydrous THF (10 mL) to a suspension of lithium

aluminum hydride (0.1 g, 2.85 mmol) in anhydrous THF (20 mL) at –10°C and stir for 20 min at –10°C. Treat the reaction mixture with 2N aqueous NaOH until a granular precipitate starts to form and filter through a pad of Celite®. Evaporate the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1, 4:1, 7:3, 3:2 and 1:1) to obtain the desired intermediate as a yellow oil (0.4 g, 99%). MS (ES+) *m/z*: 166 $(M+H)^+$.

6-Bromomethyl-benzothiazole: Dissolve benzothiazol-6-yl-methanol (0.4 g, 2.55 mmol) in diethyl ether (10 mL) and add slowly a solution of phosphorus tribromide (0.7 g, 2.55 mmol) in diethyl ether (5 mL). Stir the reaction mixture for 2 h at ambient temperature, wash with brine, dry the organic phase over anhydrous Na_2SO_4, evaporate the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1 and 4:1) to obtain the title compound as a white solid (0.5 g, 86%). MS (ES+) *m/z*: 229 $(M+H)^+$.

Preparation 153

6-Bromomethyl-2-cyclohexyl-benzothiazole



Cyclohexanecarboximidic acid ethyl ester, hydrochloride: Combine cyclohexanecarbonitrile (1.0 g, 9.20 mmol), ethanol (0.4 g, 9.20 mmol) and 4N hydrogen chloride in dioxane (8 mL) and stir the reaction mixture for 17 h at ambient temperature. Evaporate the solvent and triturate the residue with diethyl ether to obtain the desired intermediate as a white solid (1.4 g, 80%).

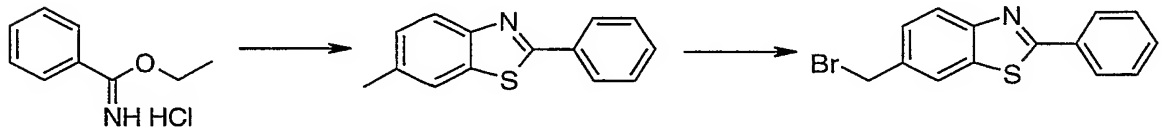
2-Cyclohexyl-6-methyl-benzothiazole: Combine 2-amino-5-methyl-benzenethiol zinc salt (1.0 g, 2.91 mmol, prepared as described in *Synth. Commun.* 1980, *10*, 167-173), cyclohexanecarboximidic acid ethyl ester hydrochloride (1.1 g, 5.82 mmol), methanol (20

mL) and reflux the reaction mixture for 17 h. Evaporate the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) to obtain the desired intermediate as a white solid (1.15 g, 85%).

6-Bromomethyl-2-cyclohexyl-benzothiazole: Combine 2-benzyl-6-methyl-benzothiazole (0.6 g, 2.42 mmol), NBS (0.5 g, 2.54 mmol), AIBN (40 mg, 0.24 mmol), carbon tetrachloride (10 mL) and reflux for 3 h. Cool the reaction mixture to ambient temperature, dilute with chloroform and wash with water. Dry the organic extracts over anhydrous Na_2SO_4, concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) to obtain the title compound as a white solid (0.4 g, 53%). MS (ES+) *m/z*: 311 $(M+H)^+$.

Preparation 154

6-Bromomethyl-2-phenyl-benzothiazole

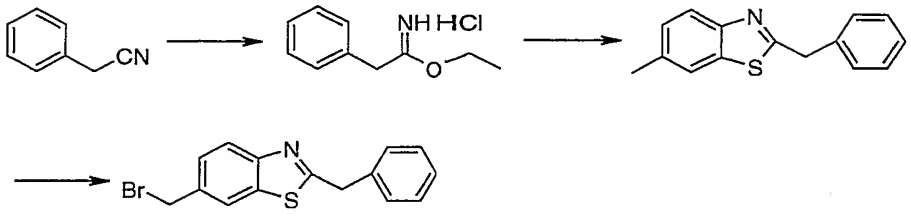


6-Methyl-2-phenyl-benzothiazole: Combine 2-amino-5-methyl-benzenethiol zinc salt (1.0 g, 2.91 mmol, prepared as described in *Synth. Commun.* 1980, *10*, 167-173), ethyl benzimidate hydrochloride (1.1 g, 5.82 mmol), methanol (20 mL), and reflux the reaction mixture for 17 h. Evaporate the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) to obtain the desired intermediate as a white solid (1.1 g, 85%). MS (ES+) *m/z*: 226 $(M+H)^+$.

6-Bromomethyl-2-phenyl-benzothiazole: Combine 6-methyl-2-phenyl-benzothiazole (0.2 g, 0.98 mmol), NBS (0.2 g, 1.02 mmol), AIBN (20 mg, 0.10 mmol), carbon tetrachloride (5 mL) and reflux for 3 h. Cool the reaction mixture to ambient temperature, dilute with chloroform and wash with water. Dry the organic extracts over anhydrous Na_2SO_4, concentrate and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1, 8:2 and 7:3) to obtain the title compound as a white solid (0.2 g, 69%).

Preparation 155

2-Benzyl-6-bromomethyl-benzothiazole



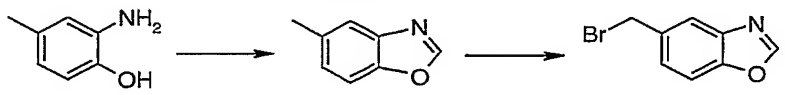
2-Phenyl-acetimidic acid ethyl ester, hydrochloride: Combine benzyl cyanide (1.0 g, 8.50 mmol), ethanol (0.4 g, 8.50 mmol) and 4N hydrogen chloride in dioxane (8 mL) and stir the reaction mixture at ambient temperature for 17 h. Evaporate the solvent and triturate the residue with diethyl ether to obtain the desired intermediate as a white solid (1.7 g, 100%).

2-Benzyl-6-methyl-benzothiazole: Combine 2-amino-5-methyl-benzenethiol zinc salt (1.0 g, 2.91 mmol, prepared as described in *Synth. Commun.* 1980, *10*, 167-173), 2-phenyl-acetimidic acid ethyl ester hydrochloride (1.16 g, 5.82 mmol), methanol (20 mL) and reflux the reaction mixture for 17 h. Evaporate the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) to obtain the desired intermediate as a white solid (1.0 g, 72%). MS (ES+) *m/z*: 240 $(M+H)^+$.

2-Benzyl-6-bromomethyl-benzothiazole: Combine 2-benzyl-6-methyl-benzothiazole (0.6 g, 2.51 mmol), NBS (0.5 g, 2.63 mmol), AIBN (40 mg, 0.25 mmol), carbon tetrachloride (10 mL) and reflux for 3 h. Cool the reaction mixture to ambient temperature, dilute with chloroform and wash with water. Dry the combined organic extracts over anhydrous Na_2SO_4, evaporate the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) to obtain the title compound as a white solid (0.2 g, 69%). MS (ES+) *m/z*: 319 $(M+H)^+$.

Preparation 156

5-Bromomethyl-benzoxazole

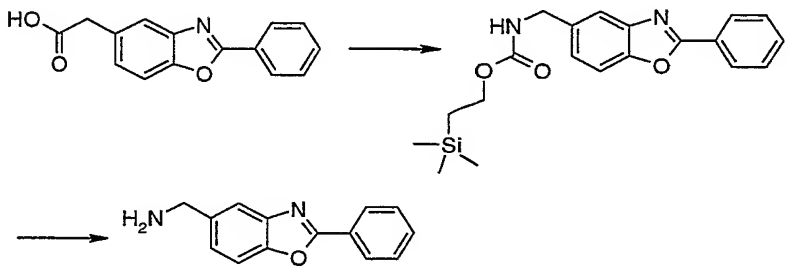


5-Methyl-benzoxazole: Combine 2-amino-4-methyl-phenol (1.0 g, 8.12 mmol), [(dimethylaminomethylene-aminomethylene)dimethylammonium chloride (Gold's reagent) (1.6 g, 9.91 mmol), anhydrous 1,4-dioxane (25 mL) and reflux for 17 h. Cool the reaction mixture to ambient temperature, evaporate the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to obtain the desired intermediate as a yellow oil (0.7 g, 65%).

5-Bromomethyl-benzoxazol: Combine 5-methyl-benzoxazole (0.5 g, 3.75 mmol), NBS (0.7 g, 3.93 mmol), AIBN (60 mg, 0.37 mmol), chloroform (10 mL) and reflux for 1 h. Cool the reaction mixture to ambient temperature, dilute with chloroform and wash with water. Dry the organic extracts over anhydrous Na_2SO_4, evaporate the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1, 4:1 and 7:3) to obtain the title compound as a white solid (0.1 g, 13%).

Preparation 157

5- Methylamino-2-phenyl-benzoxazole

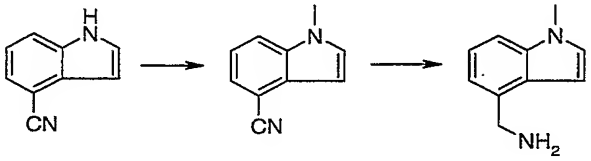


2-(Phenyl-benzoxazol-5-ylmethyl)-carbamic acid 2-trimethylsilanyl-ethyl ester: Combine (2-phenyl-benzoxazol-5-yl)-acetic acid (1.0 g, 3.95 mmol), triethylamine (0.5 g, 4.34 mmol), and anhydrous toluene (20 mL), heat to reflux and slowly add diphenylphosphoryl azide (1.2 g, 4.15 mmol) in anhydrous toluene (8 mL). Continue to reflux for 3 h, cool to ambient temperature, add 2-trimethylsilylethanol (0.9 g, 7.89 mmol) to the reaction mixture and continue to reflux for 3 h. Evaporate the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1, 4:1 and 7:3) to obtain the desired intermediate as a yellow solid (0.4 g, 26%).

5- Methylamino-2-phenyl-benzoxazole: Dissolve (2-phenyl-benzoxazol-5-yl-methyl)-carbamic acid 2-trimethylsilanyl-ethyl ester (0.4, 0.99 mmol) in anhydrous THF (5 mL) and treat with 1M tetrabutylammonium fluoride in THF (1.5 mL, 1.54 mmol). Heat the mixture at reflux for 30 min, evaporate the solvent and purify by SCX chromatography to obtain the title compound as a yellow oil (0.1 g, 27%).

Preparation 158

4-Aminomethyl-1-methylindole

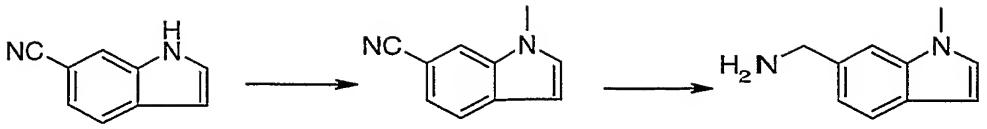


1-Methylindole-4-carbonitrile: Add slowly a solution of indole-4-carbonitrile (1.0 g, 7.04 mmol) in anhydrous DMF (5 mL) to a suspension of sodium hydride (60% dispersion in mineral oil, 0.6 g, 8.64 mmol) in anhydrous DMF (2 mL) at 0°C and warm the reaction mixture to ambient temperature. Add iodomethane (0.7 mL, 10.6 mmol) and stir the reaction for 1 h at ambient temperature. Dilute the reaction mixture with 1M aqueous NH_4OH (30 mL) and extract with diethyl ether (3 x 10 mL). Combine the organic extracts, dry over anhydrous Na_2SO_4, concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1, 4:1 and 7:3) to obtain the desired intermediate as a yellow oil (1.0 g, 87%). GC-MS *m/z*: 156 (M^+).

4-Aminomethyl-1-methylindole: Dissolve 1-methylindole-4-carbonitrile (1.0 g, 6.18 mmol) in anhydrous THF (10 mL) and add slowly to 1M lithium aluminum hydride in THF (12.4 mL, 12.37 mmol) at ambient temperature. Heat the reaction mixture at 50°C for 17 h and cool to ambient temperature. Quench the reaction mixture with water until a granular precipitate starts to form and filter through a pad of Celite®. Evaporate the solvent and purify by SCX chromatography to obtain the title compound as a yellow oil (0.9 g, 91%). GC-MS *m/z*: 160 (M^+).

Preparation 159

6-Aminomethyl-1-methylindole

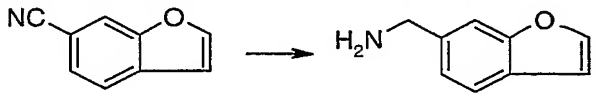


1-Methylindole-6-carbonitrile: Add slowly a solution of indole-6-carbonitrile (1.0 g, 7.04 mmol) in anhydrous DMF (5 mL) to a suspension of sodium hydride (60% dispersion in mineral oil, 0.6 g, 14.1 mmol) in anhydrous DMF (2 mL) at 0°C and warm the reaction mixture to ambient temperature. Add iodomethane (0.7 mL, 1.06 mmol) and stir the reaction mixture for 1 h at ambient temperature. Dilute the reaction mixture with 1M aqueous NH_4OH (30 mL) and extract with diethyl ether (3 x 10 mL). Combine the organic layers, dry over anhydrous Na_2SO_4, remove the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9: 1, 4:1 and 7:3) to obtain the desired intermediate as a yellow oil (1.0 g, 87%). MS (ES+) *m/z*: 156 $(M+H)^+$.

6-Aminomethyl-1-methylindole: Dissolve 1-methylindole-6-carbonitrile (0.97 g, 6.18 mmol) in anhydrous THF (10 mL) and add slowly to 1M lithium aluminum hydride in THF (1.24 mL, 1.24 mmol) at ambient temperature. Heat the reaction mixture at 50°C for 17 h and cool to ambient temperature. Quench the reaction mixture with water until a granular precipitate starts to form and filter through a pad of Celite®. Evaporate the solvent and purify by SCX chromatography to obtain the title compound as a yellow oil (0.9 g, 91%). GC-MS *m/z*: 160 (M^+).

Preparation 160

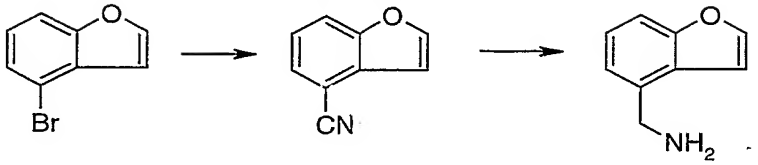
6-Aminomethyl-benzofuran



Dissolve benzofuran-6-carbonitrile (0.5 g, 3.28 mmol) in anhydrous THF (10 mL) and add slowly to 1M lithium aluminum hydride in THF (6.56 mL, 6.56 mmol) at ambient temperature. Heat the reaction mixture at 50°C for 17 h and cool to ambient temperature. Quench the reaction mixture with water until a granular precipitate starts to form and filter through a pad of Celite®. Evaporate the solvent and purify by SCX chromatography to obtain the title compound as a yellow oil (0.4 g, 79%).

Preparation 161

4-Aminomethyl-benzofuran

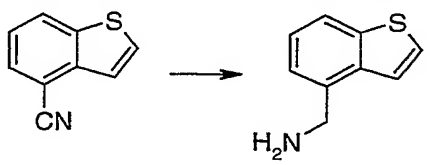


Benzofuran-4-carbonitrile: Combine 4-bromo-benzofuran (1.0 g, 5.07 mmol), copper(I) cyanide (0.9 g, 10.2 mmol), anhydrous DMF (16 mL) and reflux for 17 h. Cool the reaction mixture to ambient temperature, treat with 50% (v/v) aqueous ethylenediamine (25 mL). Extract the reaction mixture with diethyl ether (3 x 15 mL), combine the organic extracts, wash with brine (15 mL) and dry over anhydrous Na_2SO_4. Evaporate the solvent and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1 and 4:1) to obtain the desired intermediate as a colorless oil (0.3 g, 39%).

4-Aminomethyl-benzofuran: Dissolve benzofuran-4-carbonitrile (0.3 g, 1.96 mmol) in anhydrous THF (5 mL) and add slowly to 1M lithium aluminum hydride in THF (3.91 mL, 3.91 mmol) at ambient temperature. Heat the reaction mixture at 50°C for 5 h and cool to ambient temperature. Quench the reaction mixture with water until a granular precipitate starts to form and filter through a pad of Celite®. Evaporate the solvent and purify by SCX chromatography to obtain the title compound as a brown oil (0.4 g, 79%). GC-MS *m/z*: 147 (M^+).

Preparation 162

4-Aminomethyl-benzo[*b*]thiophene

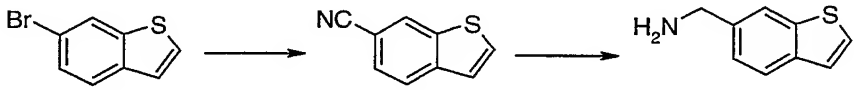


Add lithium aluminum hydride (1M solution in THF, 7.5 mL) to benzo[*b*]thiophene-4-carbonitrile (prepared as described in WO 0168653) (0.6 g, 3.8

mmol) at 0°C in THF (38 mL). After 17 h at ambient temperature, cool to 0°C and add sequentially water (1.89 mL), 2N aqueous NaOH (1.89 mL) and water (2.69 mL). Filter the solids and evaporate the filtrate to obtain the crude amine. Purify by SCX chromatography. Rinse the column with methanol, add a solution of the crude amine in methanol, wash the column with methanol and then elute with 1N ammonia in methanol. Concentrate to give the title compound (0.57 g, 93%). GC-MS *m/z*: 163 (M^+).

Preparation 163

6-Aminomethyl-benzo[*b*]thiophene

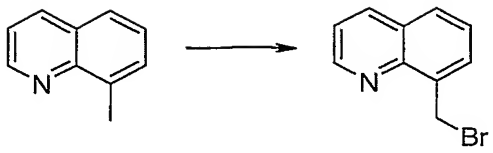


Benzo[*b*]thiophen-6-carbonitrile: Heat copper(I) cyanide (0.84 g, 9.4 mmol) and 6-bromobenzo[*b*]thiophene (prepared as described in WO 01/23381) (1.0 g, 4.7 mmol) at 160°C for 13 h. Cool the mixture to 0°C, add 33% aqueous ethylenediamine (20 mL) and dilute with ether. Wash the organic mixture with brine, dry over Na_2SO_4 and evaporate. Purify by chromatography on silica gel eluting with EtOAc/hexane (0:1 to 1:3) to give the desired intermediate (0.58 g, 78%). GC-MS *m/z*: 159 (M^+).

6-Aminomethyl-benzo[*b*]thiophene: Add 1M lithium aluminum hydride in THF (7.3 mL) to benzo[*b*]thiophene-6-carbonitrile (0.6 g, 3.6 mmol) at 0°C in THF (36 mL). After 15 h at ambient temperature, cool to 0°C and add sequentially water (1.82 mL), 2N aqueous NaOH (1.82 mL) and water (2.60 mL). Filter the solid and evaporate the filtrate to obtain the crude amine. Purify by SCX chromatography. Rinse the column with methanol, add a solution of the crude amine in methanol, wash the column with methanol and then elute with 1N ammonia in methanol. Concentrate *in vacuo* to give the title compound (0.55 g, 92%).

Preparation 164

8-Bromomethyl-quinoline



Combine 8-methyl-quinoline (1.0 g, 6.99 mmol), NBS (1.3 g, 7.13 mmol), benzoyl peroxide (6.0 mg, 0.03 mmol), carbon tetrachloride (30 mL) and reflux for 17 h. Cool the reaction mixture to ambient temperature and evaporate the solvent. Dissolve the residue in chloroform (30 mL), wash the organic solution with saturated aqueous $NaHCO_3$ (2 x 10 mL), brine (10 mL) and dry over anhydrous Na_2SO_4. Evaporate the solvent and purify by chromatography on silica gel eluting with DCM to obtain the title compound as a white solid (1.3 g, 83%). MS (ES+) *m/z*: 223 $(M+H)^+$.

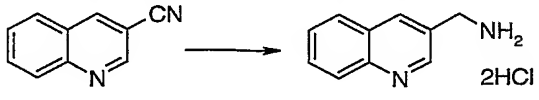
Preparation 165

2-Aminomethyl-quinoline

Combine quinoline-2-carbonitrile (0.2 g, 1.29 mmol), Raney® 3201 nickel (slurry in water, 0.05 g), 2N ammonia in methanol (10 mL) and hydrogenate at 50 psi for 15 min. Filter the reaction mixture through a pad of Celite®, remove the solvent and purify by SCX chromatography to obtain the title compound as a yellow oil (0.2 g, 98%). MS (ES+) *m/z*: 159 $(M+H)^+$.

Preparation 166

3-Aminomethyl-quinoline Dihydrochloride

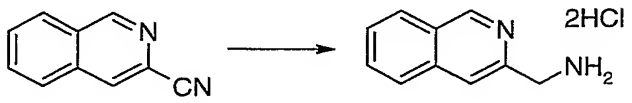


Combine quinoline-3-carbonitrile (1.0 g, 6.49 mmol), 10% Pd/C (0.2 g), 5% TFA in methanol (100 mL) and hydrogenate at 30 psi for 2 h. Filter the reaction mixture through a pad of Celite® and evaporate the solvent. Dissolve the residue in ethanol (10 mL), treat with 1N hydrogen chloride in diethyl ether (5 mL) and allow the mixture to

stand at 5°C for 18 h. Filter the precipitate, wash with ethanol and dry under *vacuo* to obtain the title compound as a white solid (0.6 g, 53%).

Preparation 167

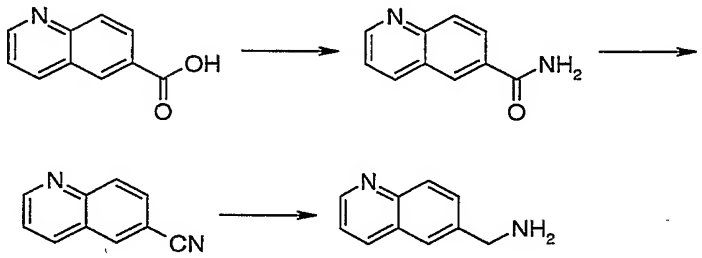
2-Aminomethyl-isoquinoline Dihydrochloride



Combine isoquinoline-3-carbonitrile (1.0 g, 6.49 mmol), 10% Pd/C (0.2 g), 5% TFA in methanol (95 mL) and hydrogenate at 30 psi for 17 h. Filter the reaction mixture through a pad of Celite® and evaporate the solvent. Dissolve the residue in ethanol (10 mL), treat with 1N hydrogen chloride in diethyl ether (5 mL) and allow to stand at 5 °C for 18 h. Filter the precipitate, wash with ethanol and dry under *vacuo* to obtain the title compound as a white solid (0.6 g, 55%).

Preparation 168

6-Aminomethyl-quinoline



6-Quinolinecarboxamide: Combine 6-quinolinecarboxylic acid (2.0 g, 11.6 mmol), 1,1-carbonyldiimidazol (3.8 g, 23.45 mmol) in DCM (50 mL) and stir at ambient temperature for 1 h. Saturate the reaction mixture with anhydrous ammonia and continue to stir for 1 h. Quench the reaction mixture with water (100 mL) and extract with chloroform (3 x 50 mL). Combine the organic extracts, dry over anhydrous Na_2SO_4 and evaporate the solvent to obtain the desired intermediate as a white solid (1.6 g, 78%).

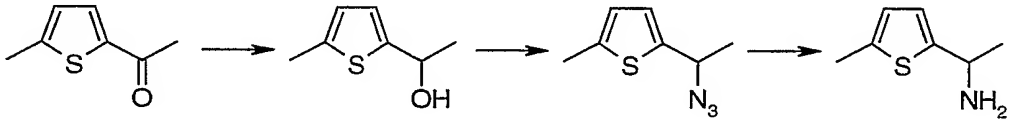
6-Quinolinecarbonitrile: Dissolve 6-quinolinecarboxamide (1.5 g, 8.95 mmol) in DCM (50 mL), add triethylamine (2.7 g, 26.8 mmol) and cool the reaction mixture to 0°C. Add trifluoroacetic acid anhydride (2.4 g, 11.16 mmol) to the reaction mixture and stir for 10

min at 0 °C. Quench the reaction mixture with water (20 mL) and separate the organic layer. Extract aqueous layer with DCM (2 x 15 mL). Combine the organic extracts and dry over anhydrous Na_2SO_4. Evaporate the solvent to obtain the desired intermediate as a white solid (1.0 g, 73%). GC-MS *m/z*: 154 (M^+).

6-Aminomethyl-quinoline: Combine 6-quinolinecarbonitrile (1.0 g, 6.49 mmol), Raney® 3201 nickel (slurry in water, 0.2 g), 2N ammonia in methanol (20 mL) and hydrogenate at 50 psi for 1 h. Filter the reaction mixture through a pad of Celite®, remove the solvent and purify by SCX chromatography to obtain the title compound as a yellow oil (0.8 g, 78%).

Preparation 169

(±)-2-(1-Aminoethyl)-5-methylthiophene



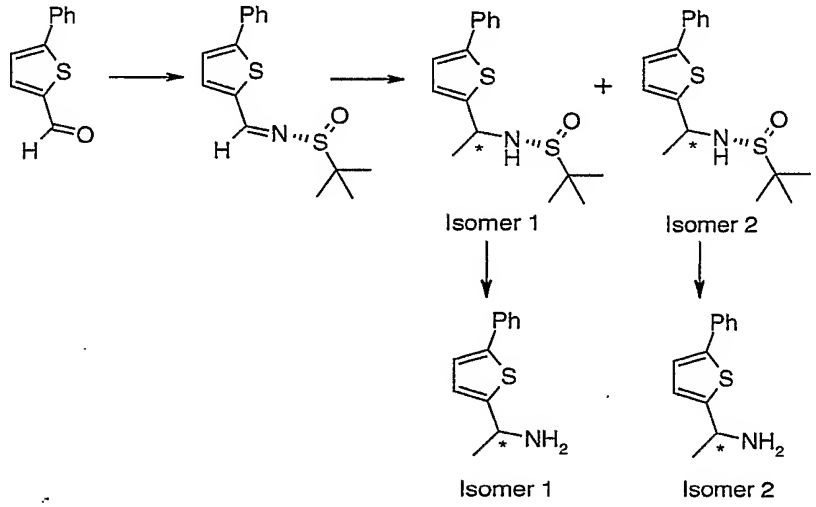
(±)-2-(1-Hydroxyethyl)-5-methylthiophene: Add sodium borohydride (270 mg, 7.13 mmol) to a solution of 2-acetyl-5-methylthiophene (1.0 g, 7.13 mmol) in methanol (40 mL). Stir the mixture for 1 h at room temperature. Remove the solvent *in vacuo* and partition the residue between water and DCM. Separate the organic phase, dry over Na_2SO_4, filter and concentrate to obtain the desired intermediate as an oil (0.995 g, 98%) that was used without further purification. GC-MS *m/z* 142 (M^+).

(±)-2-(1-Azidoethyl)-5-methylthiophene: Add DBU (1.228 g, 1.2 mL, 8.07 mmol) to a solution of (±)-2-(1-hydroxyethyl)-5-methylthiophene (0.955 g, 6.72 mmol) and diphenylphosphoryl azide (2.22 g, 1.74 mL, 8.07 mmol) in anhydrous toluene. Stir at room temperature for 18 h. Dilute the mixture with EtOAc and wash with water and 0.5N aqueous HCl. Dry the organic phase over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 19:1) to obtain the desired intermediate as an oil (0.875 g, 78%). GC-MS *m/z* 167 (M^+).

(±)-2-(1-Aminoethyl)-5-methylthiophene: Add lithium aluminum hydride (29 mg, 0.72 mmol) to a solution of (±)-2-(1-azidoethyl)-5-methylthiophene (100 mg, 0.59 mmol) in anhydrous THF (5 mL). Stir at room temperature overnight. Work-up the mixture with EtOAc and water. Filter the mixture over Celite®. Separate and wash the organic phase with brine. Dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by SCX chromatography. Rinse with DCM/methanol (1:1), load the crude mixture in methanol and elute sequentially with methanol and 1N ammonia in methanol to obtain the title compound as an oil (80 mg, 95%). GC-MS *m/z* 141 (M^+).

Preparations 170 and 171

1-(5-Phenyl-thiophen-2-yl)ethylamine, Isomers 1 and 2



***N*-[(5-Phenylthiophen-2-yl)-methylene]-2-methylpropanesulfinamide:** To a solution of 5-phenyl-2-thiophenecarboxaldehyde (1.25 g, 6.64 mmol) in anhydrous THF (50 mL), add titanium(IV) ethoxide (3.03 g, 2.78 mL, 13.28 mmol) and (*R*)-(+)-2-methyl-2-propanesulfinamide (0.965 g, 7.968 mmol) under nitrogen. Heat the reaction at 80°C overnight. Cool the mixture to room temperature and dilute with EtOAc. Add water and filter the resulting precipitate over Celite®. Separate and dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo* to obtain the desired intermediate as a yellow solid (1.93 g, 100% yield) that was used without purification.

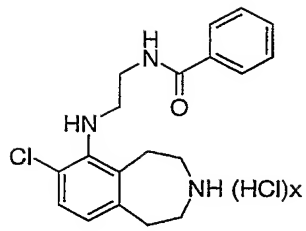
N-[1-(5-Phenylthiophen-2-yl)ethyl]-2-methylpropanesulfinamide (Isomer 1) and N-[1-(5-phenylthiophen-2-yl)ethyl]-2-methylpropanesulfinamide (Isomer 2): Add slowly methyllithium (8.1 mL, 12.92 mmol, 1.6 M solution in ether) to a solution of *N*-[(5-phenylthiophen-2-yl)-methylene]-2-methylpropanesulfinamide (1.883 g, 6.46 mmol) in anhydrous THF (50 mL) at –40°C. Warm the reaction to –20°C and stir for 2 h. Warm to 0°C and stir for an additional 2 h. Add saturated aqueous NH_4Cl and extract with EtOAc. Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (7:3 and 1:1) to obtain *N*-[1-(5-phenylthiophen-2-yl)ethyl]-2-methylpropanesulfinamide (Isomer 1) (575 mg, 30% yield) and *N*-[1-(5-phenylthiophen-2-yl)ethyl]-2-methylpropanesulfinamide (Isomer 2) (847 mg, 44% yield).

1-(5-Phenyl-thiophen-2-yl)ethylamine (Isomer 1, Preparation 170) Add 4N hydrogen chloride in dioxane (0.837 mL, 3.349 mmol) to a stirred solution of *N*-[1-(5-phenylthiophen-2-yl)ethyl]-2-methylpropanesulfinamide (Isomer 1) (515 mg, 1.675 mmol) in methanol (8 mL) at room temperature. Stir for 2 h and remove the solvent *in vacuo* to obtain a solid that was washed with ethyl ether. Dissolve the solid in DCM and wash with saturated aqueous $NaHCO_3$. Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo* to obtain the desired intermediate (236 mg, 69% yield).

1-(5-Phenyl-thiophen-2-yl)ethylamine (Isomer 2, Preparation 171) Add 4N hydrogen chloride in dioxane (1.112 mL, 4.449 mmol) to a stirred solution of *N*-[1-(5-phenylthiophen-2-yl)ethyl]-2-methylpropanesulfinamide (Isomer 2) (684 mg, 2.225 mmol) in methanol (10 mL) at room temperature. Stir for 2 h and remove the solvent *in vacuo* to obtain a solid that was washed with ethyl ether. Dissolve the solid in DCM and wash with saturated aqueous $NaHCO_3$. Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo* to obtain the desired intermediate (347 mg, 77% yield).

Example 49

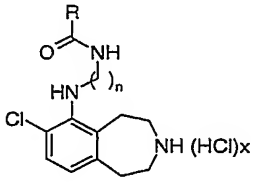
6-(2-Benzoylamino-ethylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



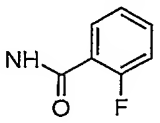
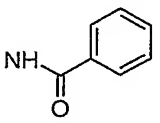
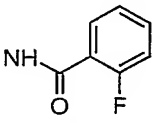
Dissolve 6-(2-amino-ethylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (70 mg, 0.208 mmol) in DCM (4 mL). Add benzoyl chloride (24 μL, 0.208 mmol), and triethylamine (44 μL, 0.312 mmol) and stir at ambient temperature for 24 h under nitrogen atmosphere. Dilute with DCM and add 1M aqueous HCl. Extract the aqueous layer with DCM. Dry the organic layer over $MgSO_4$ and concentrate in *vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 7:3 and 1:1) to obtain 6-(2-benzoylamino-ethylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine.

Use a method similar to the General Procedure 1-1, using 6-(2-benzoylamino-ethylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, to give the free base of the title compound. Use a method similar to the General Procedure 2-2 to give the title compound (77 mg, 90% overall). HPLC: $t_R = 2.64$ min (20–80% of Solvent B in 7.5 min. Solvent A: water, 0.1% TFA. Solvent B: acetonitrile, 0.1% TFA. Column: C18 Metachem, 5 micron, 4.6x50).

Examples 50-52 may be prepared essentially as described in Example 49 by using 6-(2-amino-ethylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine or 6-(3-amino-propylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate benzoyl chloride. Overall yields and MS (ES+) data are shown in the Table below.



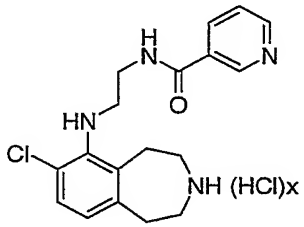
Ex.	NH-CO-R	n	Compound	Yield (%)	MS (ES+)

					m/z
50		2	7-Chloro-6-[2-(2-fluorobenzoylamino)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	40	362 $(M+H)^+$
51		3	6-(3-Benzoylamino-propylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	90	ND
52		3	7-Chloro-6-[3-(2-fluorobenzoylamino)-propylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	40	376 $(M+H)^+$

ND = Not determined

Example 53

7-Chloro-6-{2-[(pyridine-3-carbonyl)-amino]-ethylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



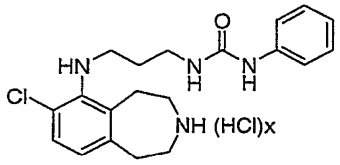
Dissolve nicotinic acid (28.2 mg, 0.23 mmol) in DCM (3 mL). Add EDC (40 mg, 0.208 mmol), HOBT (28.1 mg, 0.2081mmol) and stir at ambient temperature for 10 min. Add 6-(2-amino-ethylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (70 mg, 0.208 mmol) and stir at ambient temperature for 10 hr. Dilute with DCM, add water and extract the aqueous layer three times with DCM. Wash combined organic extracts with 1N aqueous NaOH, and brine. Dry the organic layer over $MgSO_4$, concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 1:1, 3:7 and 1:9) to obtain 7-chloro-6-{2-[(pyridine-3-carbonyl)-amino]-ethylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine.

Use a method similar to the General Procedure 1-1, using 7-chloro-6-{2-[(pyridine-3-carbonyl)-amino]-ethylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, to give the free base of the title compound. Use a method similar to

the General Procedure 2-2 to give the title compound as a solid (92 mg, 98%). HPLC: t_R= 1.38 min (20–80% of Solvent B in 7.5 min. Solvent A: water, 0.1% TFA. Solvent B: acetonitrile, 0.1% TFA. Column: C18 Metachem, 5 micron, 4.6x50).

Example 54

7-Chloro-6-[3-(3-phenyl-ureido)-propylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

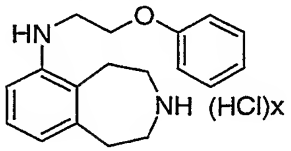


Combine phenyl isocyanate (15 μL, 0.137 mmol) and 6-(3-amino-propylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (48 mg, 0.137 mmol) in DCM and stir for 16 h. Concentrate, add DCM, filter and collect the solid to obtain 7-chloro-6-[3-(3-phenyl-ureido)-propylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (18 mg, 28%).

Use a method similar to the General Procedure 1-1, using 7-chloro-6-[3-(3-phenyl-ureido)-propylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, to give the free base of the title compound. Use a method similar to the General Procedure 2-2 to give the title compound (14 mg, 23%). MS (ES+) *m/z*: 373 $(M+H)^+$.

Example 55

6-(2-Phenoxy-ethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

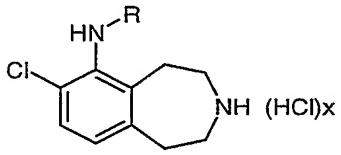


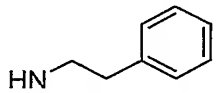
Use a method similar to the General Procedure 5-1, using 3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.23 mmol) and phenoxyethylamine (63 mg, 0.4 mmol) to give, after chromatography on silica gel eluting with hexane/EtOAc (85:15) followed by SCX chromatography, 6-(2-phenoxy-

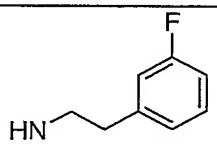
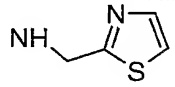
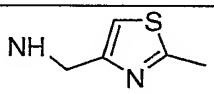
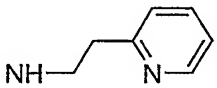
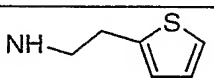
ethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil. MS (ES+) *m/z*: 379 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 6-(2-phenoxy-ethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (75 mg, 0.19 mmol). Purify by SCX chromatography to give the free base of the title compound. Use a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (ES+) *m/z*: 283 $(M+H)^+$.

Examples 56-61 may be prepared essentially as described in Example 55 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. The yields for the Step1 (General Procedure 5-1) and MS (ES+) data are shown in the Table below.



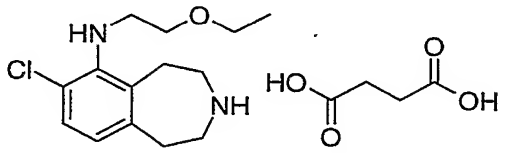
Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
56		7-Chloro-6-phenethylamino-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	47	301 $(M+H)^+$

Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
57		7-Chloro-6-(3-fluoro-phenethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	55	319 $(M+H)^+$
58		7-Chloro-6-[(thiazol-2-yl)methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	21	294 $(M+H)^+$
59		7-Chloro-6-[(2-methyl-thiazol-4-yl)methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	16	308 $(M+H)^+$
60		7-Chloro-6-(2-pyridin-2-yl-ethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	86	302 $(M+H)^+$
61		7-Chloro-6-(2-thiophen-2-yl-ethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	78	ND

ND = Not determined

Example 62

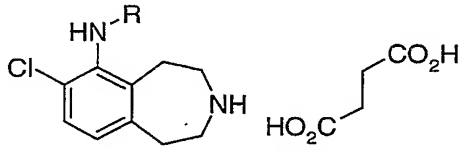
7-Chloro-6-[(2-ethoxyethyl)amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

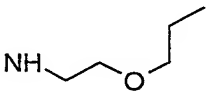
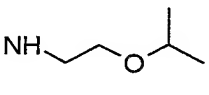
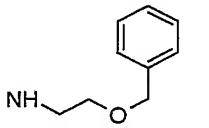
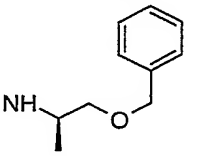
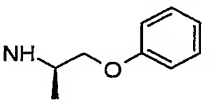


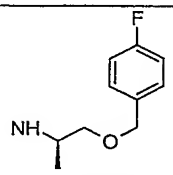
Use a method similar to the General Procedure 5-1, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.47 mmol) and 2-ethoxyethyl amine (105 µL, 1.0 mmol) to give, after chromatography on silica gel eluting with hexane/EtOAc (95:5) and additional SCX chromatography, 7-chloro-6-[(2-ethoxyethyl)amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (32 mg, 19%). MS (ES+) *m/z*: 365 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[(2-ethoxyethyl)amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (30 mg, 0.08 mmol). Purify by SCX chromatography to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound as an oil (23.8 mg, 75% over 2 steps). MS (ES+) *m/z*: 269 $(M+H)^+$.

Examples 63-68 may be prepared essentially as described in Example 62 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. The yields for the Step 1 (General Procedure 5-1), optical rotations and MS (ES+) data are shown in the Table below.



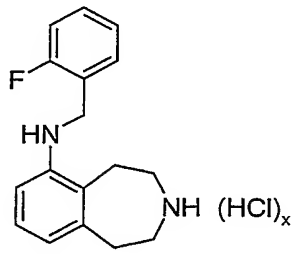
Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z.*	$[\alpha]^{20}_D$ (c, solvent)
63		7-Chloro-6-[2-(1-propoxy)ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	57	283 $(M+H)^+$	-
64		7-Chloro-6-[2-(2-propoxy)ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	75	283 $(M+H)^+$	-
65		6-(2-Benzyloxy-ethylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	37	331 $(M+H)^+$	-
66		(*R*)-6-(2-Benzyloxy-1-methyl-ethylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	15	345 $(M+H)^+$	ND
67		(*R*)-6-(2-Phenoxy-1-methyl-ethylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	15	331 $(M+H)^+$	+54.7° (c 0.5, CH_3OH)

Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z.*	$[\alpha]^{20}_D$ (c, solvent)
68		(*R*)-6-[2-(4-Fluorobenzyloxy)-1-methyl-ethylamino]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	69	363 $(M+H)^+$	+22.6° (c 0.5, CH_3OH)

ND = Not determined

Example 69

6-(2-Fluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

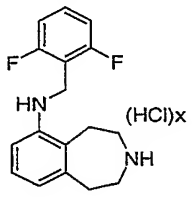


Use a method similar to the General Procedure 5-1, using 3-(2,2,2-trifluoroacetyl)-6-trifluoromethylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.26 mmol) and 2-fluorobenzylamine (88 μL, 0.77 mmol) to give, after chromatography on silica gel eluting with hexane/EtOAc (9:1), 6-(2-fluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (45 mg, 48%). MS (ES+) *m/z*: 367 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 6-(2-fluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (40 mg, 0.11 mmol). Purify by SCX chromatography to give the free base of the title compound as a yellow oil (28 mg, 94 %). Use a method similar to the General Procedure 2-2 to give the title compound as an off-white solid (29 mg, 95%). MS (ES+) *m/z*: 271 $(M+H)^+$.

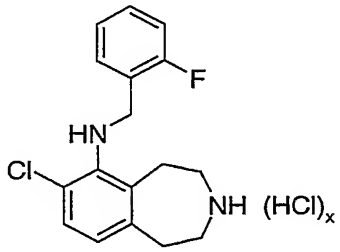
Example 70 may be prepared essentially as described in Example 69 by using 3-(2,2,2-trifluoroacetyl)-6-trifluoromethylsulfonyloxy-2,3,4,5-tetrahydro-1*H*-

benzo[*d*]azepine and 2,6-difluorobenzylamine. The yield for the Step 1 (General Procedure 5-1) and MS (ES+) data are shown in the Table below.

Ex.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
70		6-(2,6-Difluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	69	289 $(M+H)^+$

Example 71

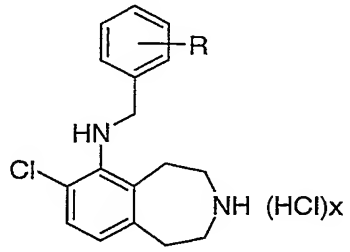
7-Chloro-6-(2-fluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the General Procedure 5-1 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-fluorobenzyl amine. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 and 4:1) to give 7-chloro-6-(2-fluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow solid. MS (ES+) *m/z*: 401 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-(2-fluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by SCX chromatography to give the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-2 to give the title compound as a light yellow solid. MS (ES+) *m/z*: 305 $(M+H)^+$.

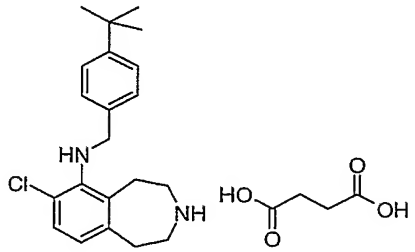
Examples 72-80 may be prepared essentially as described in Example 71 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. MS (ES+) data are shown in the Table below.



Ex.	R	Compound	MS (ES+) *m/z*
72	3-F	7-Chloro-6-(3-fluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	305 $(M+H)^+$
73	4-F	7-Chloro-6-(4-fluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	305 $(M+H)^+$
74	2,3-diF	7-Chloro-6-(2,3-difluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	323 $(M+H)^+$
75	3,4-diF	7-Chloro-6-(3,4-difluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	323 $(M+H)^+$
76	3,5-diF	7-Chloro-6-(3,5-difluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	323 $(M+H)^+$
77	3,4,5-triF	7-Chloro-6-(3,4,5-trifluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	341 $(M+H)^+$
78	3-CF_3	7-Chloro-6-(3-trifluoromethyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	355 $(M+H)^+$
79	3,5-diCF_3	7-Chloro-6-[3,5-bis(trifluoromethyl)benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	423 $(M+H)^+$
80	4-$O(CH_2)_2N(CH_3)_2$	7-Chloro-6-{4-[2-(*N*,*N*-dimethylamino)ethoxy]benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	374 $(M+H)^+$

Example 81

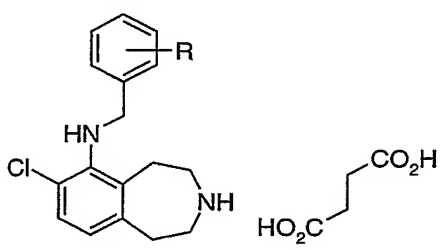
6-(4-*tert*-Butylbenzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the General Procedure 5-1 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (300 mg, 0.7 mmol) with 4-(*tert*-butyl)benzyl amine (375 μL, 2.1 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (95:5) followed by SCX chromatography to give 6-(4-*tert*-butylbenzylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (240 mg, 78%). MS (ES+) *m/z*: 439 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 6-(4-*tert*-butylbenzylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (235 mg, 0.54 mmol). Purify by SCX chromatography to give the free base of the title compound (161 mg, 87%). Use a method similar to the General Procedure 2-1 to give the title compound as an off-white gum (190 mg, 88%). MS (ES+) *m/z*: 343 $(M+H)^+$.

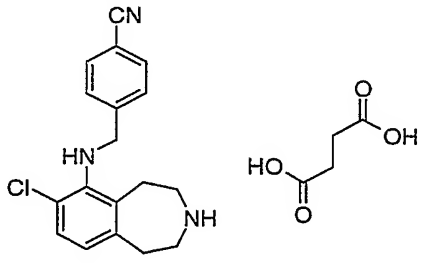
Examples 82-88 may be prepared essentially as described in Example 81 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. MS (ES+) data are shown in the Table below.



Ex.	R	Compound	MS (ES+) *m/z*
82	3-*t*-Bu	6-(3-*tert*-Butylbenzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	343 $(M+H)^+$
83	4-OCF_3	7-Chloro-6-(4-trifluoromethoxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	371 $(M+H)^+$
84	4-F,3-CF_3	7-Chloro-6-[(4-fluoro-3-trifluoromethyl)benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	373 $(M+H)^+$
85	4-F,3-OCH_3	7-Chloro-6-[(4-fluoro-3-methoxy)benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	321 $(M+H)^+$
86	4-Ph	7-Chloro-6-(4-phenylbenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	363 $(M+H)^+$
87	4-OPh	7-Chloro-6-(4-phenoxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	379 $(M+H)^+$
88	4-SO_2CH_3	7-Chloro-6-(4-methanesulfonyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	365 $(M+H)^+$

Example 89

7-Chloro-6-(4-cyanobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



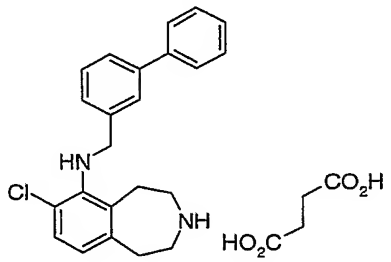
Use a method similar to the General Procedure 5-1 to react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (504 mg, 1.2 mmol), 4-cyanobenzylamine (476 mg, 3.6 mmol), palladium(II) acetate (29 mg, 0.1 mmol), BINAP (148 mg, 0.2 mmol) and cesium carbonate (540 mg, 1.7 mmol) in

toluene (5 mL). Purify by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 1:1) to give 7-chloro-6-(4-cyanobenzylamino)-3-(2,2,2-trifluoroacetyl)–2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a white gum (108 mg, 22%). MS (ES+) *m/z*: 408 $(M+H)^+$.

Use a method similar to the General Procedure 1-2 to deprotect 7-chloro-6-(4-cyanobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (98 mg, 0.2 mmol). Purify by preparative liquid chromatography eluting with a gradient of water/acetonitrile (19:1 to 1:19) to give the free base of the title compound (31 mg, 42%). MS (ES+) *m/z*: 312 $(M+H)^+$. Use a method similar to the General Procedure 2-1, using 7-chloro-6-(4-cyanobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (31 mg, 0.1 mmol) to give the title compound as a beige solid (41 mg, 95%). MS (ES+) *m/z*: 312 $(M+H)^+$.

Example 90

7-Chloro-6-(3-phenyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



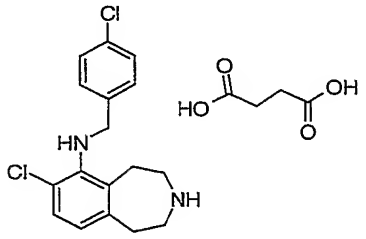
Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.3 g, 0.706 mmol) with 3-phenyl-benzylamine (0.388 g, 2.117 mmol) using palladium(II) acetate (32 mg, 0.141 mmol), tris(dibenzylideneacetone)dipalladium(0) (65 mg, 0.070 mmol), BINAP (264 mg, 0.424 mmol) and cesium carbonate (460 mg, 1.412 mmol) in toluene (12 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 19:1) to give 7-chloro-6-(3-phenyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (0.257 g, 79%). MS (ES+) *m/z*: 459 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-(3-phenyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (237 mg, 0.516 mmol), to give the free base of the title compound as an oil (188 mg, 100%) that was used without further purification.

Use a method similar to the General Procedure 2-1, using 7-chloro-6-(3-phenyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (188 mg, 0.518 mmol) to give the title compound as a white solid (191 mg, 77%). MS (ES+) *m/z*: 363 $(M+H)^+$.

Example 91

7-Chloro-6-(4-chlorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

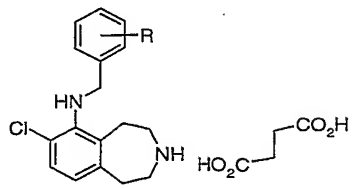


Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (700 mg, 1.6 mmol) with 4-chlorobenzylamine (354 mg, 2.5 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) and then SCX chromatography to give 7-chloro-6-(4-chlorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (459 mg, 69%). MS (ES+) *m/z*: 417 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[1-(4-chlorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to give the free base of the title compound. MS (ES+) *m/z*: 321 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to obtain the title compound.

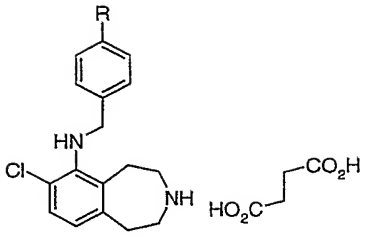
Examples 92-98 may be prepared essentially as described in Example 91 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-

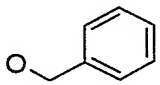
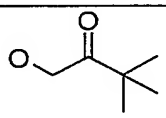
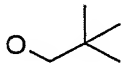
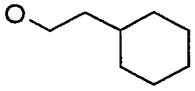
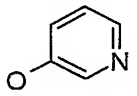
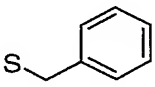
benzo[*d*]azepine and the appropriate amine. The yields for the Step 1 (General Procedure 5-3) and MS (ES+) data are shown in the Table below.



Ex.	R	Compound	Yield (%)	MS (ES+) *m/z*
92	3-Cl	7-Chloro-6-(3-chlorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	45	321 $(M+H)^+$
93	3-Cl,4-F	7-Chloro-6-(3-chloro-4-fluoro-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	90	339 $(M+H)^+$
94	2-Cl,4-F	7-Chloro-6-(2-chloro-4-fluoro-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	75	339 $(M+H)^+$
95	3-OCH_3	7-Chloro-6-(3-methoxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	84	316 $(M+H)^+$
96	2-F,4-CH_3	7-Chloro-6-(2-fluoro-4-methyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	53	319 $(M+H)^+$
97	3-OCF_3	7-Chloro-6-(3-trifluoromethoxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	85	371 $(M+H)^+$
98	3-Cl,4-OCH_3	7-Chloro-6-(3-chloro-4-methoxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	100	351 $(M+H)^+$

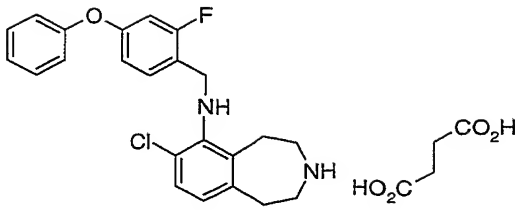
Examples 99-106 may be prepared essentially as described in Example 91 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. The yields for the Step 1 (General Procedure 5-3) and MS (ES+) data are shown in the Table below.



Ex.	R	Compound	Yield (%)	MS (ES+) *m/z*
99		7-Chloro-6-(4-benzyloxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	87	393 $(M+H)^+$
100		7-Chloro-6-[4-(3,3-dimethyl-2-oxo-butoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	20	401 $(M+H)^+$
101		7-Chloro-6-[4-(2,2-dimethylpropoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	23	373 $(M+H)^+$
102		7-Chloro-6-[4-(2-cyclohexylethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	61	413 $(M+H)^+$
103		7-Chloro-6-[4-(1*H*-pyrazol-1-yl)benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	36	353 $(M+H)^+$
104		7-Chloro-6-[4-(pyridin-3-yloxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	42	380 $(M+H)^+$
105		6-(4-Benzylthio-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	21	409 $(M+H)^+$

Example 106

7-Chloro-6-(2-fluoro-4-phenoxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

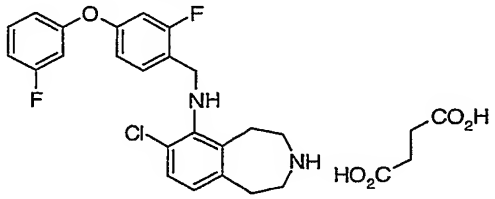


Using a method similar to the General Procedure 5-3, couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.1 g, 2.5 mmol) with 2-fluoro-4-phenoxy-benzylamine (550 mg, 2.5 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) and then SCX chromatography to obtain 7-chloro-6-(2-fluoro-4-phenoxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. MS (ES+) *m/z*: 493 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-(2-fluoro-4-phenoxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to give the free base of the title compound (468 mg, 47% overall). MS (ES+) *m/z*: 397 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to obtain the title compound.

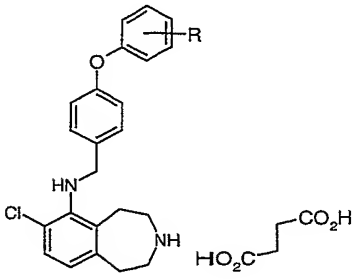
Example 107

7-Chloro-6-[2-fluoro-4-(3'-fluorophenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the Example 106, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (426 mg, 1.0 mmol) and 2-fluoro-4-(3'-fluorophenoxy)-benzylamine (340 mg, 1.4 mmol) to give the free base of the title compound (162 mg, 39%). MS (ES+) *m/z*: 415 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to obtain the title compound.

Examples 108-121 may be prepared essentially as described in Example 107 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. The yields for the Step 1 (General Procedure 5-3) and MS (ES+) data are shown in the Table below.



5

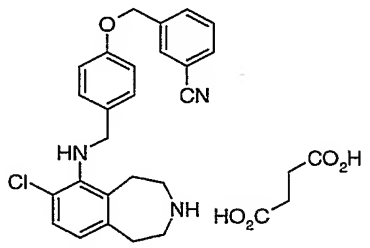
Ex.	R	Compound	Yield (%)	MS (ES+) *m/z*
108	2-F	7-Chloro-6-[4-(2'-fluorophenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	44	397 $(M+H)^+$
109	3-F	7-Chloro-6-[4-(3'-fluorophenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	23	397 $(M+H)^+$
110	4-F	7-Chloro-6-[4-(4'-fluorophenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	50	397 $(M+H)^+$
111	3-Cl	7-Chloro-6-[4-(3'-chlorophenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	45	413 $(M+H)^+$
112	3,5-diF	7-Chloro-6-[4-(3',5'-difluorophenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	36	415 $(M+H)^+$
113	4-CH_3	7-Chloro-6-[4-(4'-methylphenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	54	393 $(M+H)^+$
114	3-CH_3	7-Chloro-6-[4-(3'-methylphenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	45	393 $(M+H)^+$
115	2-CH_3	7-Chloro-6-[4-(2'-methylphenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	54	393 $(M+H)^+$
116	3-^{i}Pr	7-Chloro-6-[4-(3'-isopropylphenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	49	421 $(M+H)^+$
117	2-^{i}Pr	7-Chloro-6-[4-(2'-	40	421

		isopropylphenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate		$(M+H)^+$
118	2-CN	7-Chloro-6-[4-(2'-cyanophenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	79	404 $(M+H)^+$

Ex.	R	Compound	Yield (%)	MS (ES+) *m/z*
119	3-CN	7-Chloro-6-[4-(3'-cyanophenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	37	404 $(M+H)^+$
120	2-CF_3	7-Chloro-6-[4-(2'-trifluoromethyl-phenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	30	447 $(M+H)^+$
121	3-CF_3	7-Chloro-6-[4-(3'-trifluoromethyl-phenoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	37	447 $(M+H)^+$

Example 122

7-Chloro-6-[4-(3'-cyanobenzyloxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

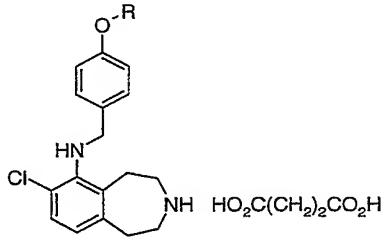


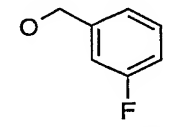
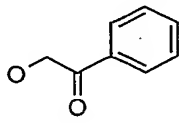
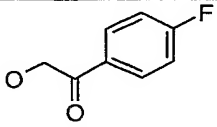
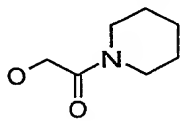
Mix 7-chloro-6-(4-hydroxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (150 mg, 0.38 mmol), 3-cyanobenzyl bromide (90 mg, 0.46 mmol), podwered potassium carbonate (105 mg, 0.76 mmol), powdered potassium iodide (6.6 mg, 0.04 mmol) and acetone (30 mL). Stir and heat to reflux under nitrogen for 16 hr. Dilute with acetone, filter, concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 4:1) to obtain 7-chloro-6-[4-(3'-cyanobenzyloxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (72.4 mg, 37%). MS (ES+) *m/z* 514 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[4-(3'-cyanobenzyloxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to give the free base of the title compound (42 mg, 71%). MS (ES+)

m/z: 418 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to obtain the title compound.

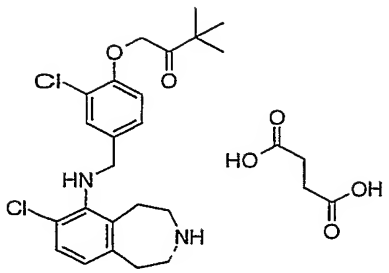
Examples 123-126 may be prepared essentially as described in Example 122 by using 7-chloro-6-(4-hydroxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropiate bromide. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	O-R	Compound	Yield (%)	MS (ES+) *m/z*
123		7-Chloro-6-[4-(3'-fluorobenzyloxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	75	411 $(M+H)^+$
124		7-Chloro-6-[4-(2-oxo-2-phenyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	45	421 $(M+H)^+$
125		7-Chloro-6-[4-(2-oxo-2-(4-fluorophenyl)-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	17	439 $(M+H)^+$
126		7-Chloro-6-[4-(2-oxo-2-piperidin-1-yl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	44	428 $(M+H)^+$

Example 127

7-Chloro-6-[3-chloro-4-(3,3-dimethyl-2-oxo-butoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

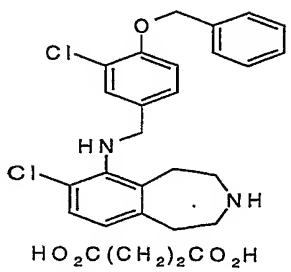


Use a method similar to the General Procedure 4-1 to react 7-chloro-6-(3-chloro-4-hydroxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (438 mg, 1.01 mmol) and 1-bromopinacolone (217 mg, 1.21 mmol). Purify by chromatography on silica gel eluting with EtOAc/hexane (1:4) to give 7-chloro-6-[3-chloro-4-(3,3-dimethyl-2-oxo-butoxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (441 mg, 82%). MS (ES+) *m/z*: 531 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[3-chloro-4-(3,3-dimethyl-2-oxo-butoxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (441 mg, 0.83 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (93:7) to give the free base of the title compound (278 mg, 95%). MS (ES+) *m/z*: 435 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to give the title compound.

Example 128

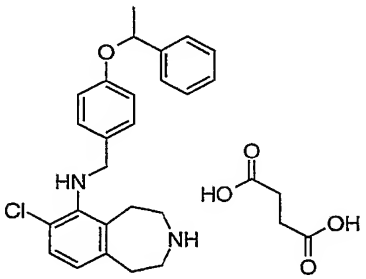
7-Chloro-6-(3-chloro-4-benzyloxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



The title compound may be prepared essentially as described in Example 127, using 7-chloro-6-(3-chloro-4-hydroxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and benzyl bromide (64%). MS (ES+) *m/z*: 427 $(M+H)^+$.

Example 129

(±)-7-Chloro-6-[4-(1-phenyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

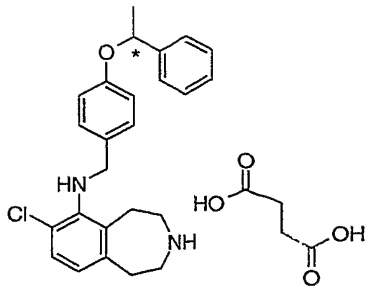


Use a method similar to the General Procedure 5-3, to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (851 mg, 2.0 mmol) and (±)-4-(1-phenyl-ethoxy)-benzylamine (721 mg, 2.6 mmol). Purify by chromatography on silica gel eluting with EtOAc/hexane (1:8) to give (±)-7-chloro-6-[4-(1-phenyl-ethoxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (702 mg, 69%). MS (ES+) *m/z*: 503 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect (±)-7-chloro-6-[4-(1-phenyl-ethoxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (702 mg, 1.40 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (92:8) to give the free base of the title compound (368 mg, 65 %). MS (ES+) *m/z*: 407 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to obtain the title compound.

Examples 130 and 131

(-)-7-Chloro-6-[4-(1-phenyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate and (+)-7-Chloro-6-[4-(1-phenyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

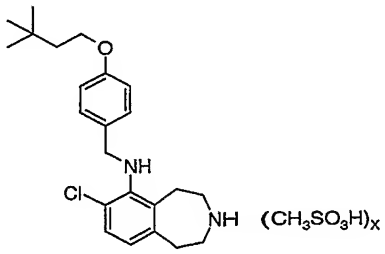


Separate the two enantiomers of Example 129 by chiral HPLC [Chiralcel OJ-H column, acetonitrile/methanol (20:80) with 0.2% DMEA; flow rate 1 mL/min; Isomer 1: t_R=5.0 min, Isomer 2: t_R=6.5 min].

Use a method similar to the General Procedure 2-1 to prepare the succinate of each enantiomer: (-)-7-chloro-6-[4-(1-phenyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate, $[\alpha]^{20}_D$ –17.4° (c 0.5, CH_3OH), and (+)-7-chloro-6-[4-(1-phenyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate, $[\alpha]^{20}_D$ +18.2° (c 0.5, CH_3OH).

Example 132

7-Chloro-6-[4-(3,3-dimethylbutoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Mesylate

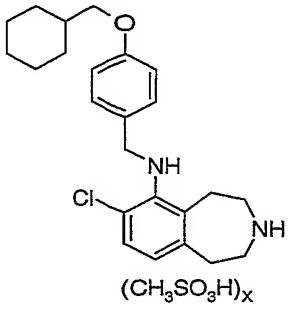


Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (426 mg, 1.0 mmol) and 4-(3,3-dimethylbutoxy)-benzylamine (325 mg, 1.5 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) and then SCX chromatography to obtain 7-chloro-6-[4-(3,3-dimethylbutoxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. MS (ES+) *m/z*: 483 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[4-(3,3-dimethylbutoxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to give the free base of the title compound (161 mg, 42% overall). MS (ES+) *m/z*: 387 $(M+H)^+$. Use a method similar to the General Procedure 2-4 to obtain the title compound.

Example 133

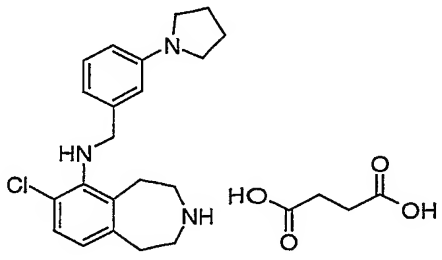
7-Chloro-6-(4-cyclohexylmethoxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Mesylate



The title compound may be prepared essentially as described in Example 132, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-cyclohexylmethoxy-benzylamine (27% yield, MS (ES+) *m/z* 399 $(M+H)^+$).

Example 134

7-Chloro-6-(3-pyrrolidinyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

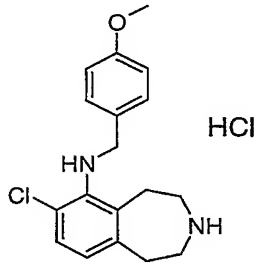


Use a method similar to the General Procedure 5-1, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (300 mg, 0.7 mmol) and 3-(pyrrolidin-1-yl)benzylamine (300 mg, 1.7 mmol) to give, after chromatography on silica gel eluting with hexane/EtOAc (19:1, 9:1, 4:1 and 3:2), 7-chloro-6-(3-pyrrolidinyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (195 mg, 62%). MS (ES+) *m/z*: 452 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-(3-pyrrolidinyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (195 mg, 0.43 mmol). Purify by SCX chromatography to give the free base of the title compound (136 mg, 89%). Use a method similar to the General Procedure 2-1, using 7-chloro-6-(3-pyrrolidinyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (130 mg, 0.37 mmol), to give the title compound as an off-white gum (111 mg, 61%). MS (ES+) *m/z*: 356 $(M+H)^+$.

Example 135

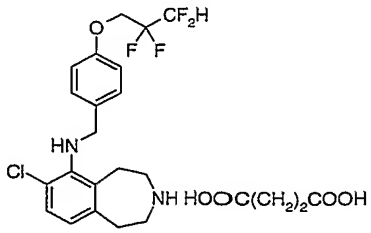
6-(4-Methoxybenzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a similar method to the General Procedure 1-1, using 6-(4-methoxybenzylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.1 g, 0.24 mmol) to give the free base of the title compound. Use a similar method to the General Procedure 2-2 to give the title compound (75 mg, 80%). HRMS calcd for $C_{18}H_{21}ClN_2O$ 317.1421, found 317.1410.

Example 136

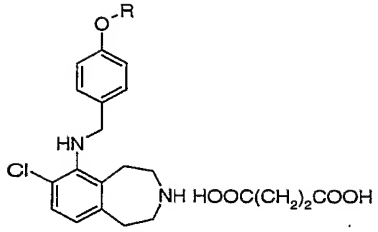
7-Chloro-6-[4-(2,2,3,3-tetrafluoropropoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

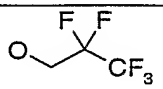
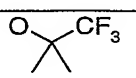


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (500 mg, 1.2 mmol) with 4-(2,2,3,3-tetrafluoropropoxy)-benzylamine (835 mg, 3.5 mmol) in toluene (10 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1, 5:1 and 3:1) followed by SCX chromatography [pre-wash column with methanol followed by DCM, load material dissolved in DCM, then elute with DCM/2M ammonia in methanol (1:1) and concentrate *in vacuo*] to obtain 7-chloro-6-[4-(2,2,3,3-tetrafluoropropoxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (600 mg, 99%).

Use a method similar to the the General Procedure 1-3 to deprotect 7-chloro-6-[4-(2,2,3,3-tetrafluoropropoxy)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (600 mg, 1.2 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99:1 to 90:10) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound (390 mg, 62 %). MS (ES+) *m/z*: 417 $(M+H)^+$.

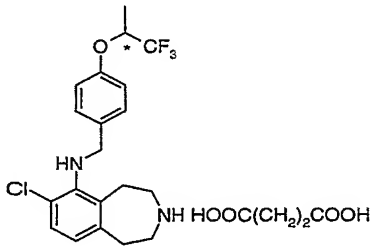
Examples 137-138 may be prepared essentially as described in Example 136 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	O-R	Compound	Yield (%)	MS (ES+) *m/z*
137		7-Chloro-6-[4-(2,2,3,3,3-pentafluoropropoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	45	435 $(M+H)^+$
138		7-Chloro-6-[4-(2,2,2-trifluoro-1,2-dimethyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	66	413 $(M+H)^+$

Examples 139 and 140

(-)-7-Chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate and (+)-7-Chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (500 mg, 1.2 mmol) with (±)-4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzylamine (515 mg, 2.3 mmol) in toluene (10 mL). Purifyby chromatography on silica gel eluting with hexane/EtOAc (10:1, 5:1 and 3:1) followed by SCX chromatography [pre-wash column with methanol followed by DCM, load material dissolved in DCM, then elute with DCM/2M ammonia in methanol (1:1) and concentrate *in vacuo*] to give (±)-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (530 mg, 90%). GC-MS *m/z*: 494 (M^+).

Use a method similar to the General Procedure 1-3 to deprotect (±)-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (520 mg, 1.1 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99:1 to 90:10) to give (±)-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Use a method similar to the General Procedure 2-1 to obtain (±)-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate.

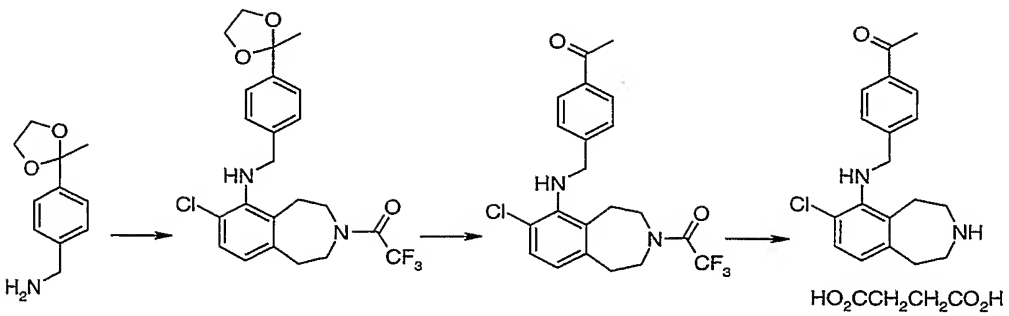
Separate the two enantiomers of (±)-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate by normal phase chiral chromatography (Chiralpak AD 8x30 cm, elute with 85:15 heptane/3A ethanol with 0.2% DMEA).

Use a method similar to the General Procedure 2-1 to obtain (-)-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate [137 mg, 71% recovery, 98% ee (Chiralpak AD, 4.6x150 mm, eluent: 85:15 heptane/isopropanol with 0.2% DMEA, 0.6 mL/min)]. MS (ES+) *m/z*: 399 $(M+H)^+$. $[\alpha]^{20}_D$ –7.9° (c 0.5, MeOH).

Use a method similar to the General Procedure 2-1 to obtain (+)-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate [133 mg, 69% recovery, 97% ee (Chiralpak AD, 4.6x150 mm, eluent: 85:15 heptane/isopropanol with 0.2% DMEA, 0.6 mL/min)]. MS (ES+) *m/z*: 399 $(M+H)^+$. $[\alpha]^{20}_D$ +9.2° (c 0.5, MeOH).

Example 141

6-(4-Acetyl-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.47 mmol) with 4-(2-methyl-[1,3]dioxolan-2-yl)-benzylamine (prepared by following the procedure described in *J. Med. Chem.* 1978, *21*, 507) (182 mg, 0.94 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 19:1 and 9:1) to give 6-{4-(2-methyl-[1,3]dioxolan-2-yl)benzylamino}-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (150 mg, 68%). GC-MS *m/z* 468 (M^+).

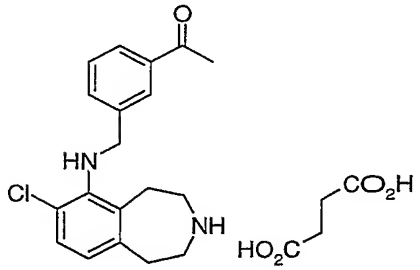
Dissolve 6-{4-(2-methyl-[1,3]dioxolan-2-yl)benzylamino}-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (150 mg, 0.32 mmol) in methanol (5 mL) and add 1N aqueous HCl (1 mL). Stir the solution at ambient temperature for 2 h. Remove the solvent, dissolve the residue in DCM and wash with saturated aqueous $NaHCO_3$. Dry the organic phase over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1, 17:3 and 4:1) to obtain 6-(4-acetyl-benzylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (107 mg, 79%). GC-MS *m/z* 424 (M^+).

Use a method similar to the General Procedure 1-2, using 6-(4-acetyl-benzylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.23 mmol), to give the free base of the title compound as an oil (76 mg, 99%) that was used without further purification.

Use a method similar to the General Procedure 2-1, using 6-(4-acetyl-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (76 mg, 0.23 mmol), to give the title compound as a white solid (102 mg, 97%). MS (ES+) *m/z*: 329 $(M+H)^+$.

Example 142

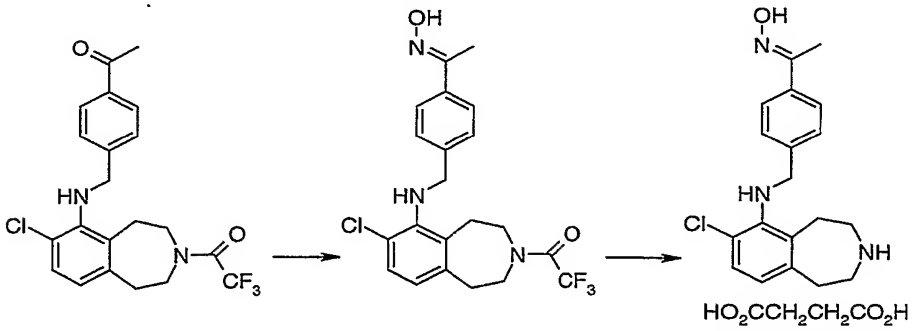
6-(3-Acetylbenzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to Example 141, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-(2-methyl-[1,3]dioxolan-2-yl)-benzylamine (prepared by following the procedure described in *J. Med. Chem.* 2000, *43*, 3315), to give the title compound as a solid. MS (ES+) *m/z*: 329 $(M+H)^+$.

Example 143

7-Chloro-6-[4-(1-hydroxyiminoethyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Add hydroxylamine hydrochloride (19 mg, 0.27 mmol) and pyridine (0.04 mL, 0.54 mmol) to a solution of 6-(4-acetylbenzylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (115 mg, 0.27 mmol) in ethanol (10 mL). Heat the mixture to reflux for 2 h. Remove the solvent *in vacuo* and partition the residue between DCM and 0.1N aqueous HCl. Dry the organic phase over Na_2SO_4, filter and concentrate. Dissolve the oil into the minimum amount of ether and add hexane to precipitate the solid. Filter to obtain 7-chloro-6-[4-(1-hydroxyiminoethyl)-benzylamino]-

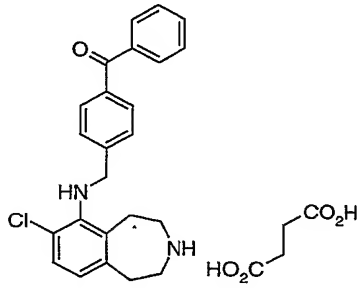
3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a solid (112 mg, 94%) that was used without further purification. MS (ES+) *m/z*: 440 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[4-(1-hydroxyiminoethyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.23 mmol), to give 7-chloro-6-[4-(1-hydroxyiminoethyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (61 mg, 78%) that was used without further purification.

Use a method similar to the General Procedure 2-1, using 7-chloro-6-[4-(1-hydroxyiminoethyl)benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine(58 mg, 0.17 mmol) to give the title compound as a white solid (68 mg, 87%). MS (ES+) *m/z*: 344 $(M+H)^+$.

Example 144

6-(4-Benzoyl-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



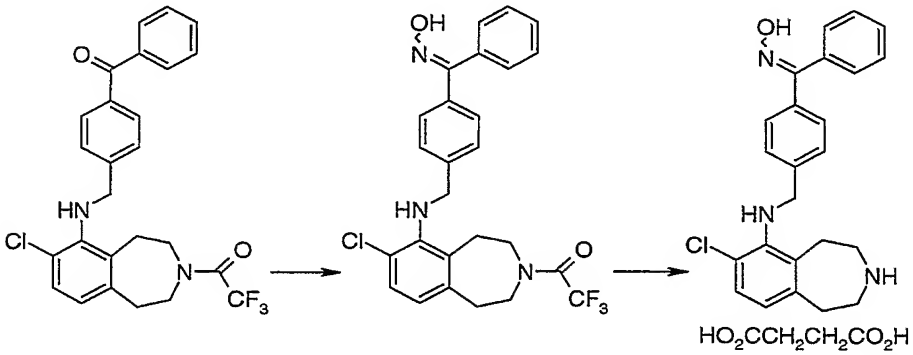
Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (272 mg, 0.64 mmol) with 4-(aminomethyl)benzophenone (prepared by following the procedure described in *J. Biol. Chem.* 1993, *268 (19)*, 14230) (270 mg, 1.3 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1, 17:3 and 4:1) to give 6-(4-benzoyl-benzylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (300 mg, 96%).

Use a method similar to the General Procedure 1-2, using 6-(4-benzoyl-benzylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (80 mg, 0.16 mmol), to give 6-(4-benzoyl-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (47 mg, 73%) that was used without further purification.

Use a method similar to the General Procedure 2-1, using -(4-benzoyl-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (45 mg, 0.11 mmol), to give the title compound as a white solid (37 mg, 63%). MS (ES+) *m/z*: 391 $(M+H)^+$.

Example 145

7-Chloro-6-[4-(1-hydroxyiminobenzyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Add hydroxylamine hydrochloride (52 mg, 0.75 mmol) and pyridine (0.1 mL) to a solution of 6-(4-benzoyl-benzylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (91 mg, 0.19 mmol) in ethanol (10 mL). Heat the mixture to reflux overnight. Remove the solvent *in vacuo* and partition the residue between DCM and 0.1N aqueous HCl. Dry the organic phase over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 4:1 and 3:1) to give 7-chloro-6-[4-(1-hydroxyiminobenzyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a mixture of E/Z isomers (93 mg, 99%).

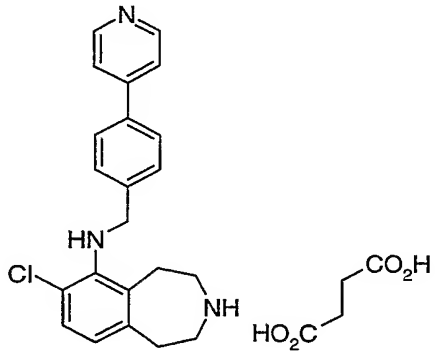
Use a method similar to the General Procedure 1-2, using 7-chloro-6-[4-(1-hydroxyiminobenzyl)benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (97 mg, 0.19 mmol), to give 7-chloro-6-[4-(1-hydroxyiminobenzyl)-

benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (68 mg, 87%) that was used without further purification.

Use a method similar to the General Procedure 2-1, using 7-chloro-6-[4-(1-hydroxyiminobenzyl)benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (65 mg, 0.16 mmol), to give the title compound as a white solid (67 mg, 80%). MS (ES+) *m/z*: 406 $(M+H)^+$.

Example 146

7-Chloro-6-[4-(pyridin-4-yl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



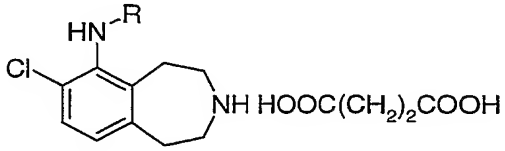
Use a method similar to the General Procedure 5-3, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (178 mg, 0.426 mmol) and a solution of 4-(pyridin-4-yl)-benzylamine (116 mg, 0.63 mmol) in THF/toluene (1:1, 8 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 7:3 and 1:1) to give 7-chloro-6-[4-(4-pyridin-4-yl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (120 mg, 63%). MS (ES+) *m/z*: 460 $(M+H)^+$.

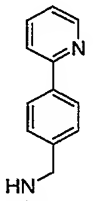
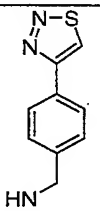
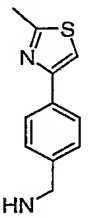
Use a method similar to the General Procedure 1-2, using 7-chloro-6-[4-(pyridin-4-yl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (153 mg, 0.33 mmol), to give 7-chloro-6-[4-(pyridin-4-yl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (110 mg, 91%) that was used without further purification.

Use a method similar to the General Procedure 2-1, using 7-chloro-6-[4-(pyridin-4-yl)-

benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (105 mg, 0.289 mmol) to give the title compound as a white solid (123 mg, 88%). MS (ES+) *m/z*: 364 $(M+H)^+$.

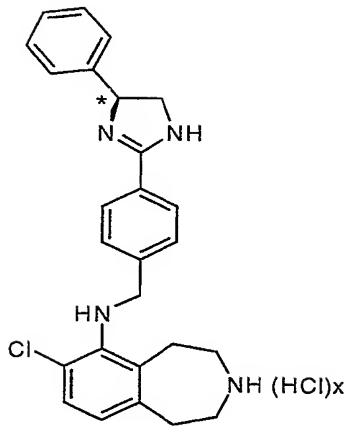
Examples 147-149 may be prepared essentially as described in Example 146 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
147		7-Chloro-6-[4-(pyridin-2-yl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	32	364 $(M+H)^+$
148		7-Chloro-6-[4-(1,2,3-thiadiazol-4-yl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	23	371 $(M+H)^+$
149		7-Chloro-6-[4-(2-methylthiazol-4-yl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	22	384 $(M+H)^+$

Example 150

(-)-7-Chloro-6-[4-(4-phenyl-4,5-dihydro-1*H*-imidazol-2-yl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

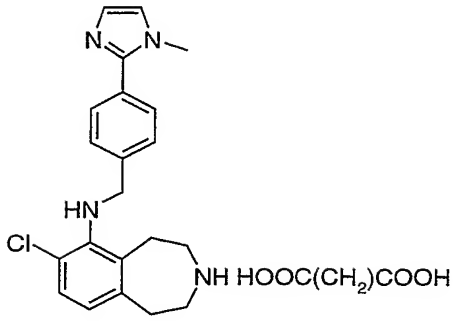


Mix 7-chloro-6-(4-cyanobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200mg, 0.49 mmol, 1.0 equiv.), 1-(*R*)-phenyl-ethane-1,2-diamine (600 mg, 4.4 mmol, prepared as described in *J. Org. Chem.* 1997, 62, 3586) and *p*-toluenesulfonic acid monohydrate (102 mg, 0.53 mmol) in a sealed tube equipped with a magnetic stirrer. Heat the mixture to 200°C for 16 h. Cool the mixture to ambient temperature. Dilute with DCM (50 mL) and wash with saturated aqueous $NaHCO_3$ (10 mL). Collect the organic fraction and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (98:2 to 80:20).

Use a method similar to the General Procedure 2-3 to give title compound as the hydrochloride. Use reverse phase HPLC [Column: Symmetry C18, 10x300 mm, flow = 25 mL/min, water with 0.1% TFA / Acetonitrile (9:1 to 2:3)] followed by SCX chromatography to obtain the free base of the title compound. Use a method similar to the General Procedure 2-3 to obtain the title compound (38 mg, 16%). MS (ES+) *m/z*: 431 $(M+H)^+$. $[\alpha]^{20}_D$ -20° (c 0.5, MeOH).

Example 151

7-Chloro-6-[4-(1-methyl-1*H*-imidazol-2-yl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

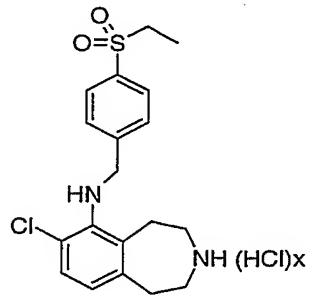


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (455 mg, 1.1 mmol) with 4-(1-methyl-1*H*-imidazol-2-yl)-benzylamine (240 mg, 1.3 mmol) in toluene (8 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1, 5:1 and 3:1) followed by SCX chromatography [pre-wash column with methanol followed by DCM, load material dissolved in DCM, then elute with DCM/2M ammonia in methanol (1:1) and concentrate *in vacuo*] to obtain 7-chloro-6-[4-(1-methyl-1*H*-imidazol-2-yl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (429 mg, 93%). MS (ES+) *m/z*: 463 $(M+H)^+$.

Use a method similar to the General Procedure 1-3 to deprotect 7-chloro-6-[4-(1-methyl-1*H*-imidazol-2-yl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99:1 to 90:10) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound (350 mg, 73 %). MS (ES+) *m/z*: 367 $(M+H)^+$.

Example 152

7-Chloro-6-(4-ethanesulfonyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



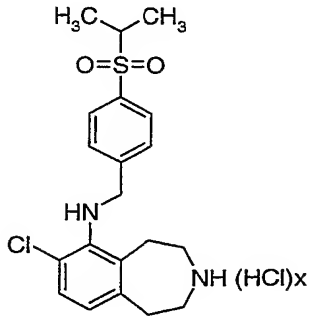
Use a method similar to the General Procedure 5-2, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.2 g, 0.35 mmol) and 4-ethanesulfonyl-benzylamine (0.2 g, 1.06 mmol) to give 7-chloro-6-(4-ethanesulfonyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil.

Use a method similar to the General Procedure 1-1 to obtain the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-2 to form the hydrochloride salt. Purify by reverse phase preparative HPLC (Zorbax SB-Phenyl 21.2x250 mm, 5 micron, 22 mL/min of 0.1% HCl in water/acetonitrile (9:1 to 1:1) over 30 min, detector at 230 nm) to obtain the title compound as a white solid (57 mg, 36%).

MS (ES+) *m/z*: 379 $(M+H)^+$.

Example 153

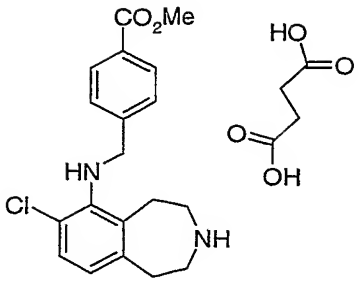
7-Chloro-6-[4-(2-propanesulfonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



The title compound may be prepared essentially as described in Example 152, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-(2-propanesulfonyl)-benzylamine(11% yield, MS (ES+) *m/z* 393 $(M+H)^+$).

Example 154

7-Chloro-6-(4-methoxycarbonyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

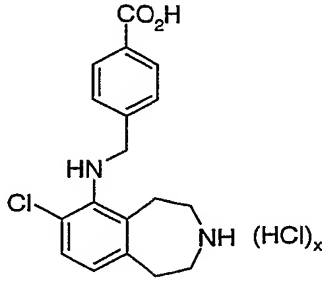


Treat 4-aminomethyl-benzoic acid methyl ester hydrochloride (0.2 g, 0.71 mmol) with K_2CO_3 (1.0 g, 0.71 mmol) in a mixture of toluene/water (1:1, 2 mL). Separate the organic layer, dry over anhydrous Na_2SO_4 and use as a toluene solution for the next step. Use a method similar to the General Procedure 5-2, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.1 g, 0.24 mmol) and 4-aminomethyl-benzoic acid methyl ester (0.2 g, 0.71 mmol) to give 7-chloro-6-(4-methoxycarbonyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil.

Use a method similar to the General Procedure 1-1 to obtain the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-1 to obtain the title compound as a white solid (20 mg, 18%). MS (ES+) *m/z*: 345 $(M+H)^+$.

Example 155

6-(4-Carboxy-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



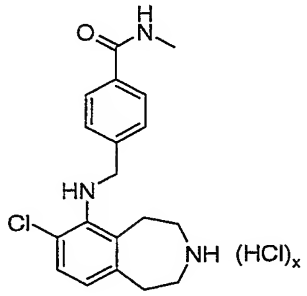
Combine 7-chloro-6-(4-methoxycarbonyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (70 mg, 0.16 mmol), potassium carbonate (0.87 g, 6.3 mmol), methanol (2 mL), water (2 mL) and heat at 50°C for 3 h. Purify by SCX

chromatography to obtain 6-(4-carboxy-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil.

Use a method similar to the General Procedure 2-2 to form the hydrochloride salt. Purify by reverse phase preparative HPLC [Zorbax SB-Phenyl 21.2x250 mm, 5 micron, 22 mL/min of 0.1% HCl in water/acetonitrile (9:1 to 1:1) over 30 min, detector at 230 nm] to obtain the title compound as a white solid (30 mg, 46%). MS (ES+) *m/z*: 331 $(M+H)^+$.

Example 156

7-Chloro-6-(4-methylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

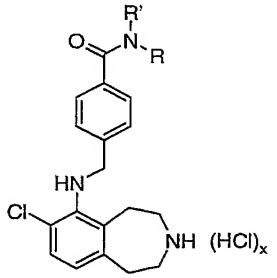


Combine 3-(*tert*-butoxycarbonyl)-6-(4-carboxy-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.1 g, 0.3 mmol), methylamine hydrochloride (31 mg, 0.46 mmol), triethylamine (0.1 g, 0.9 mmol), HATU (0.2 g, 0.5 mmol), anhydrous DMF (3 mL) and stir at ambient temperature for 17 h. Partition the reaction mixture between brine (5 mL) and diethyl ether (5 mL), separate the organic layer and dry over anhydrous Na_2SO_4. Evaporate the solvent to obtain 3-(*tert*-butoxycarbonyl)-7-chloro-6-(4-methylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (0.1 g, 93%). MS (ES+) *m/z*: 344 $(M+H\text{-}Boc)^+$.

Use a method similar to the General Procedure 1-5 and purify the residue by SCX chromatography to obtain the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-2 to form the hydrochloride salt. Purify by reverse phase preparative HPLC [Zorbax SB-Phenyl 21.2x250 mm, 5 micron, 22 mL/min

of 0.1% HCl in water/acetonitrile (9:1 to 1:1) over 30 min, detector at 230 nm] to obtain the title compound as a white solid (0.9 g, 65%). MS (ES+) *m/z*: 344 $(M+H)^+$.

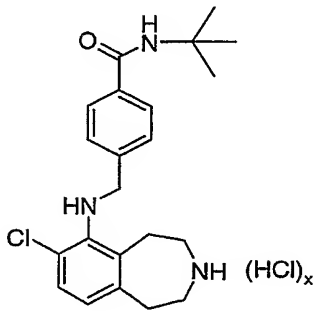
Examples 157-158 may be prepared essentially as described in Example 156 by using 3-(*tert*-butoxycarbonyl)-6-(4-carboxy-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	R	R'	Compound	Yield (%)	MS (ES+) *m/z*
157	Me	Me	7-Chloro-6-(4-dimethylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	51	358 $(M+H)^+$
158	*i*-Pr	H	7-Chloro-6-(4-isopropylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	56	372 $(M+H)^+$

Example 159

6-(4-*tert*-Butylcarbamoyl-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the General Procedure 5-2, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.2 g, 0.35 mmol) and 4-aminometyl-N-*tert*-butyl-benzamide (0.2 g, 1.06 mmol), to give